Biosimilars: A Revolution for Biologics in the Pharmaceutical Industry

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by

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Certification Statement

This is to certify that the project titled “Biosimilars: A Revolution for Biologics in the Pharmaceutical Industry” submitted for the partial fulfillment of the requirements for the degree of Bachelor of Pharmacy from the Department of Pharmacy, BRAC University constitutes my own work under the supervision of Professor Eva Rahman Kabir, Ph.D, Chairperson, Department of Pharmacy, BRAC University. Throughout the project I have given appropriate credit where I have used the language, ideas or writings of another.

Signed

_____

Counter signed by the supervisor

_____

Dedicated to Eva Miss

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Firstly, I would like to express how grateful I am to God Almighty for keeping me and my loved ones in good health and giving me the strength to stay on course with my ambitions through all hardships. It is only with His blessings and mercy that I am able to have come this far today.

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“The woods are lovely, dark and deep
But I have promises to keep
And miles to go before I sleep.”

Abstract

The high demand for and resulting financial success of biopharmaceutical products over the last three decades have seen the door open for close copies of these biological products. Popularly termed as biosimilars, these products hold immense potential for the pharmaceutical industry in terms of their applications and benefits. Biosimilars also pose to be of great promise to the Bangladesh pharmaceutical industry, with the commitment of drastically reducing its dependence on foreign imports of biopharmaceutics to meet local demand. Biosimilars have the additional advantage of requiring an abbreviated and streamlined approval process by a recognized regulatory body and are commercialized only after they have undergone clinical evaluation to verify that they are highly similar to already approved reference products. This paper seeks to provide an overview of biosimilar drugs and collate all relevant published data to assess the weight of available evidence that this new frontier holds promise for development in the drug industry. Furthermore, it aims to investigate the prospects of biosimilar development, employment and education within Bangladesh.

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List of acronyms

AAM: Association for Accessible Medicines

BPCIA: Biologics Price Competition and Innovation Act

BQ: Biologic Qualifier

DGDA: Directorate General of Drug Administration

EMA: European Medicines Agency

EU: European Union

GaBi: Generics and Biosimilars Initiative

IFPMA: International Federation of Pharmaceutical Manufacturers & Associations

INN: International Non-proprietary Name

NCBs: Non Comparable Biologics

SBPs: Similar Biotherapeutic Products

TRIPs: Trade- Related Aspects of Intellectual Property Rights

US: United States

USFDA: United States Food and Drug Administration

WTO: World Trade Organization

WHO: World Health Organization

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1. Introduction

The market for biologics and biosimilars is at a crossroads. Biotherapeutic medication are large molecule drugs which function by targeted disruption, stimulation or substitution of complex inter-protein, inter-cell and protein-cell interactions within a patient's body (IFPMA, 2016). They are drugs originating from living cell systems via highly complex processes and constitute of active ingredients such as antibodies (Appendix A1), hormones (Appendix A2), insulin (Appendix A3) and cytokines (Appendix A4). The popularity of biotherapeutical products have continued to rise due to their strong reputation in treating several life threatening and chronic diseases. Unfortunately, manufacturing of these products entails high costs and the maintenance of stringent conditions, limiting their access and availability to patients across the world, particularly those residing in developing countries (WHO, 2009). They are also vulnerable to patent expiration, the first generation of these drugs having been manufactured in the 1980s (Sekhon and Saluja, 2011).The high costs and challenges of developing novel biotech products have led pharmaceutical companies to attempt at replicating existing products to maintain a steady stream of such biologics in the development pipeline. These follow on biological products or biosimilars are defined by the World Health Organization as products which are "similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product" (WHO, 2009). The Biologics Price Competition and Innovation Act (BPCIA) signed into law by President Obama in 2010 defines biosimilars as compounds possessing a "high degree of similarity to their biological compound pioneer or innovator drug (Appendix A5), but with the possibility of presenting small differences in components of clinically inactive molecule" (Bas and Castillo, 2016).There is an inherent requirement for these products to have their licensing based on prior information regarding the safety and efficacy of their originator or reference products (WHO, 2009). Since this abbreviated pathway utilizes knowledge from the reference product, the approval process is supposed to eliminate the need for unnecessary and unethical testing of the drugs in animals and humans (Kozlowski, Woodcock et al. 2011). This new class of drugs therefore aims to provide similar acute or chronic therapeutic response as their biological counterparts, without demonstrating a significant difference in efficacy, purity, potency (Appendix A6) and safety of administration.

1.1 Background of Biologics and Biosimilars

While the manufacture of biologics in pharmaceutical industries began in the early 1980s (Epstein, Ehrenpreis et al. 2014), their financial success and presence of a "patent cliff" (a steady decline in sales as the biologic nears the expiry of its patent) made the need for follow-on biologics inevitable. The first biosimilar product, a human growth hormone named Omnitrope, was authorized for marketing in Europe by the EMA (European Medicines Agency) in April 2006 (Johnson, 2016). A follow on biologic of Amgen's Neupogen, was approved by the EMA in the same year. This was closely followed by the approval of the first monoclonal antibody (mAb) biosimilar (Inflectra, a follow on biologic of infliximab) in 2013 (Epstein, Ehrenpreis et al. 2014). Technological advancements and newly designed regulatory pathways saw the United States biosimilar industry steadily gain traction, with the US FDA approval of Zarzio (filgrastim), a biosimilar to Amgen's Neupogen, in 2015 (USFDA, 2015). Figure 1.1 illustrates the timeline of biosimilars approval.

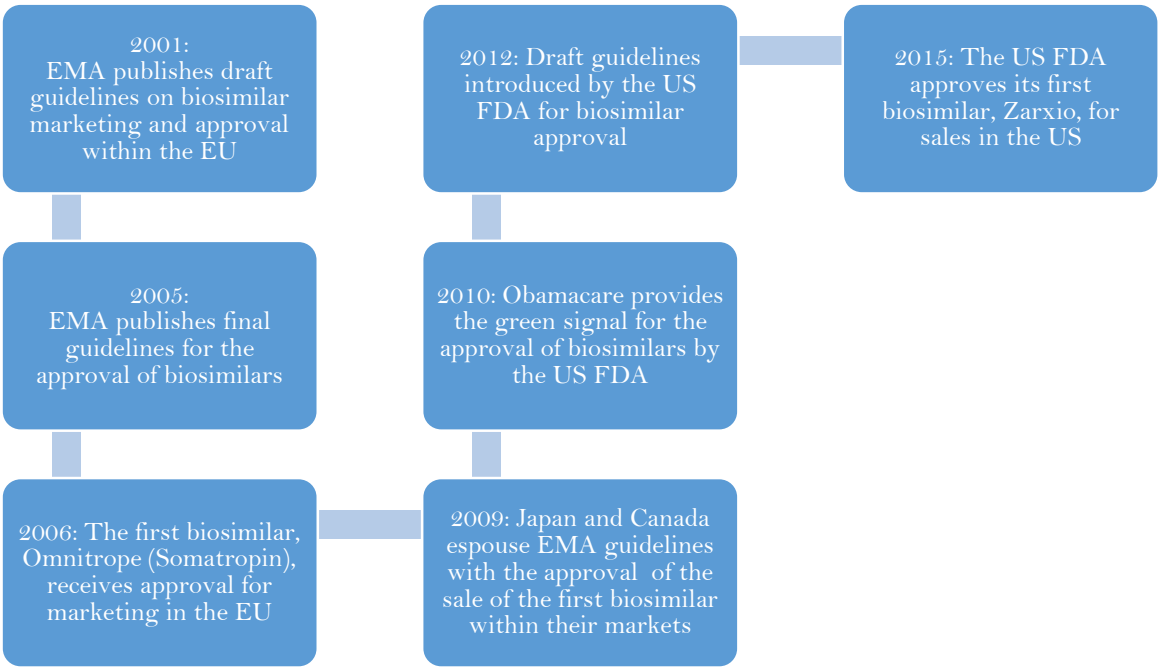

Figure 1.1 Biosimilars approval timeline (Adapted from Kumar, 2016)

Since then, around 14 more biosimilars have been approved in Europe, the products mainly centred on the biologic analogs of somatropin, epoetin alfa, and filgrastim. Three more

biosimilar products were approved in the US in 2016, the products being biosimilars of infliximab, etanercept and adalimumab (Stanton, 2016).Below Table 1.1 shows the timeline of biosimilars approved/rejected between 2006 and 2010.

Table 1.1 Timeline of Biosimilars (2006-2010) (Sekhon and Saluja 2011)

Biosimilar	Reference	Approval/Rejection Year
Omnitrope	Somatotropin	2006*
Valtropin	Somatotropin	2006*
Binocrit	Epoetin alpha	2007*
Epoetin alpha	Epoetin alpha	2007*
Hexal		
Abseamed	Epoetin alpha	2007*
Silapo	Epoetin zeta	2007*
Retacrit	Epoetin zeta	2007*
Filgrastim	Filgrastim	2008*
Ratiopharm		
Ratiograstim	Filgrastim	2008*
Biograstim	Filgrastim	2008*
Tevagrastim	Filgrastim	2008*
Filgrastim hexal	Filgrastim	2009*
Zarzio	Filgrastim	2009*
Nivestim	Filgrastim	2010*
Alpheon	Roferon - A	2006**

Human insulin	Humulin	2007**

*** Approved**

**** Rejected**

1.2 Brief Outline of Biologics and Biosimilars

Almost 200 biologic medicines have been commercialized by July 2016. The year 2017 promises to see biologics holding their position within seven of the global top ranking pharmaceuticals and constitute about 30 percent of other pharmaceuticals undergoing development (Lybecker, 2016). With the increasing medical and commercial success of recombinant proteins and monoclonal antibodies (Appendix A7), a large number of pharmaceutical companies have strived to become key players in the biologics field. Furthermore, the range of biotherapeutic therapies have also since expanded to include nanobodies (Appendix A8), soluble receptors, fusion proteins, immuno-therapies (Appendix A9), synthetic vaccines and immunoconjugates (Appendix A10) as a result of the contributions of new technologies and an improved understanding of cell line production, protein identification, expression and engineering (Muller, 2013). Pharmaceutical companies are encouraged by several reasons to move to a more biologics oriented industry. Firstly, biologics possess the capability to bind with target sites which tend to be elusive or inaccessible to small molecule drugs. This can be related with protein-protein interactions involving flat surfaces with fewer charged regions. Secondly, biologics hold highly propitious commercial potential. An investigation by the research group Evaluate Pharma in 2012 showed that there was an astounding growth in the share of biologics in the aggregate sales of prescriptions and over the counter medication from 12 percent in 2004 to 19 percent in 2011.These biologics are estimated to preside over a large portion of total sales by the year 2017 (EvaluatePharma, 2012). Thirdly, there is a better overall economic return delivered by biological drugs as opposed to that of small molecule drugs. An investigation by the KMR Group in 2009 showed that, compared to their small molecule alternatives, the financial return per patient undergoing treatment with biologics is higher and the biologics themselves display a better performance at all phases of development. The research group also showed that a larger number of biologics (24.4%) that underwent preclinical testing eventually attained commercialization compared to that of small

molecule drugs (7.1%). Biologics are further promoted due to their ease of patent procurement and relatively less competition faced from biosimilars once their patents become void (Muller, 2013).

While the market for biosimilars has seen strong advancements in the United States and European countries, it is steadily gaining traction in countries with preexisting biologicals manufacturing industries and enterprises (Morton, Stern et al. 2016). A paper by Grant Thornton India states how an estimated 21 biological products having a market net worth $50 billion will lose patent (Appendix A11) protection in USA alone between the years 2009 and 2019 (Thornton, 2013). Countries such as Bangladesh with limited health budget, strong drug policies and a lower income earning population strongly seek to benefit from the rapid growth of these products within the local industry (Hossain, Rahman et al. 2013). Furthermore, an increase in demand for highly valued biologicals such as cardiovascular, antiasthma tic, anticancer and anti-diabetic medication has pushed pharmaceutical giants within South Asia to undertake a more holistic approach towards biosimilar development. Internationally recognized regulatory bodies (such as the USFDA, WHO, EMEA and IFPMA) offer an abbreviated and streamlined approval process for biosimilars, which facilitates their commercialization if they can be shown to be highly similar to already approved reference products. This creates a potential opening for developing countries like Bangladesh into several international pharma markets such as that of the U.S and EU.

It is however, important to understand that biosimilars are not identifiable with generic versions of newly innovative drugs, and therefore do not dictate therapeutic equivalence by default. While the term “generic” medication is utilized to identify chemical small molecule drugs possessing structural and therapeutic equivalence to a reference product (usually one whose patent period has reached expiration), biologics are harder to anatomically characterize. Biologics are a hundred to thousand times larger in size than synthetic small molecule drugs, possessing several hundred amino acids biochemically combined in a definite sequence (Sekhon and Saluja, 2011). There are several more challenges to the production of these products compared to conventional generic drugs, owing mainly to their complex large molecular structure (Mellstedt, Niederwieser et al. 2007). The differences between small molecule drugs and biologics have been summarized in Table 1.2 below.

Table 1.2 Differences between small molecule drugs and biological drugs (Adapted from (Declerck, 2012) and (Lybecker, 2016))

	Small molecule drugs	**Biological drugs**
Size	- Single molecule, hence small - Low molecular weight	- combination of closely related molecules, hence large - Large molecular weight
Structure	Simple, well defined, regardless of manufacturing process	Complex (heterogeneous), defined by exact manufacturing process
Modification	Well defined	Wider range of options
Stability	Stable	Unstable, sensitive to external conditions
Characterisation	Can be characterised completely	Cannot be characterised completely because of molecular composition and heterogeneity
Immunogenicity	Usually non-immunogenic	Immunogenic
Manufacturing	- Produced by chemical synthesis - Foreseeable chemical process - Duplicate copy can be made	- Produced in living cell culture - Difficult to control process from starting material to final API - Impossible to ensure duplicate copy
Susceptibility to contamination during manufacture	Low	High

Sensitivity to physical factors (heat,light)	Low	High
Clinical behaviour	Well defined mode of action	Complex modes of action
Species	Interdependent	Specific
Absorption	More rapid	Slower
Distribution	High	Limited
Metabolism	Metabolized to active and non-active metabolites	Broken down to endogenous amino acids
Disposition	Rarely target mediated	Mostly target mediated
Half-life	Shorter	Longer

Process related or structural variations between a biosimilar and its reference biologic could lead to drastic changes in the effectiveness and safety profile in the biosimilar product. This expresses an even greater risk in the case for more complex biologics where the drug mechanisms may not be fully understood, as in the case of monoclonal antibodies. Furthermore, variations in the age, sex, gender, etc parameters of the targeted patient groups may lead to different responses to the same biotherapeutic utilized (IFPMA, 2013). A holistic understanding of the differentiation between small molecular, biological and biosimilar drugs have been described in Table 1.3 below.

Table 1.3 Differences between small molecule, generic, biological and biosimilar drugs (Zelenetz, Ahmed et al. 2011)

	Pharmaceutical industry		**Biopharmaceutical industry**	**Biosimilar industry**
Parameter	**Small molecule drug**	**Generic drug**	**Biological drug**	**Biosimilar drug**
Synthesis	Production of original chemical formula	Copy from the original chemical formula	Manufactured in a living system, usually through recombinant DNA technology	Development derived from the original biological molecule
Size	100–1000 Da	100–1000 Da	10.000–300.000 Da	10.000–300.000 Da
Glycosylation process	Zero	Zero	Several	Several
Molecular structure	Simple	Simple	Complex	Complex
Ability to generate immunity	Low	Low	Medium - High	Medium - High
Drug development time	7-10 years	1-3 years	10 – 15 years	6-9 years
Characterization via	N/A	There are techniques to	N/A	No identification technique for

analysis in laboratory		identify similarity to the original drug		equality of the molecule Clinical studies are needed

2. Critical Variables of Biologics and Biosimilars

Biosimilars possess unique characteristics with regard to small molecule generic drugs which pharmacists and clinicians are required to understand in order to ensure these medications are used safely and optimally. Major topics in the biosimilar formulary review include the evaluation of clinical parameters (interchangeability (Appendix A12), immunogenicity, clinical data), information on product manufacture, product characteristics (naming, labeling) and institutional considerations (pharmacovigilance, patient education).

2.1. The Evolving Regulatory Landscape of Biosimilars

The European Medicines Agency (EMA) was the first regulatory authority to set guidelines for biosimilars in 2005, a year before the first biosimilar was approved. The member states of the EU holds the power of implementing any regulations with regard to the manufacture, development and authorization of biosimilar products. This framework was followed by those developed by the World Health Organization (WHO) in 2009, which authorized globally accepted conditions for the introduction of safe, effective and quality similar biotherapeutic products (SBPs). The main goal of WHO's regulatory framework was to assist as well as ensure that local regulatory bodies followed the international standards of biotherapeutic production. Other countries gradually adopted these guidelines as their own, while few others authorized their own guidelines based on the existing models. In 2009, Japan and Korea released their own regulatory frameworks for biosimilars (Nellore, 2010). Countries like Australia took up the European Union (EU) guidelines without any alterations, while Malaysia and Singapore adjusted theirs to meet the standards set by the EMA guidelines. Countries such as Brazil and Cuba adopted WHO's guidelines as a foundation for their own biosimilar regulations.Countries continue to set their own regulations based on the current trends such as India which released their their guidelines later in 2012. The US was a late entrant in the biosimilar regulation pathway introduction, with their approval for biological products being made through the Public Health Service Act. The Biologics Price Competition and Innovation Act (BPCIA) was signed in 2010 as part of the Patient Protection and Affordable Care Act, which created a new licensure pathway for biosimilars with the backing of the United States Food and Drug Administration (US FDA). The BPCIA ensured the availability of drugs at affordable prices for the public, and bolstered innovation by companies producing originator biologics. From its

first biosimilar approval in 2015 to 2017, four biosimilars have been sanctioned in USA for the treatment of 23 indications (with the fifth biosimilar being recently approved in April) (Mattina, 2017). Canada also issued their guidelines in 2010 under the approval of their federal authority, Health Canada (Krishnan, Mody et al. 2015). Figure 2.1 below illustrates the approval of biosimilar regulations in various countries between 2004 and 2016.

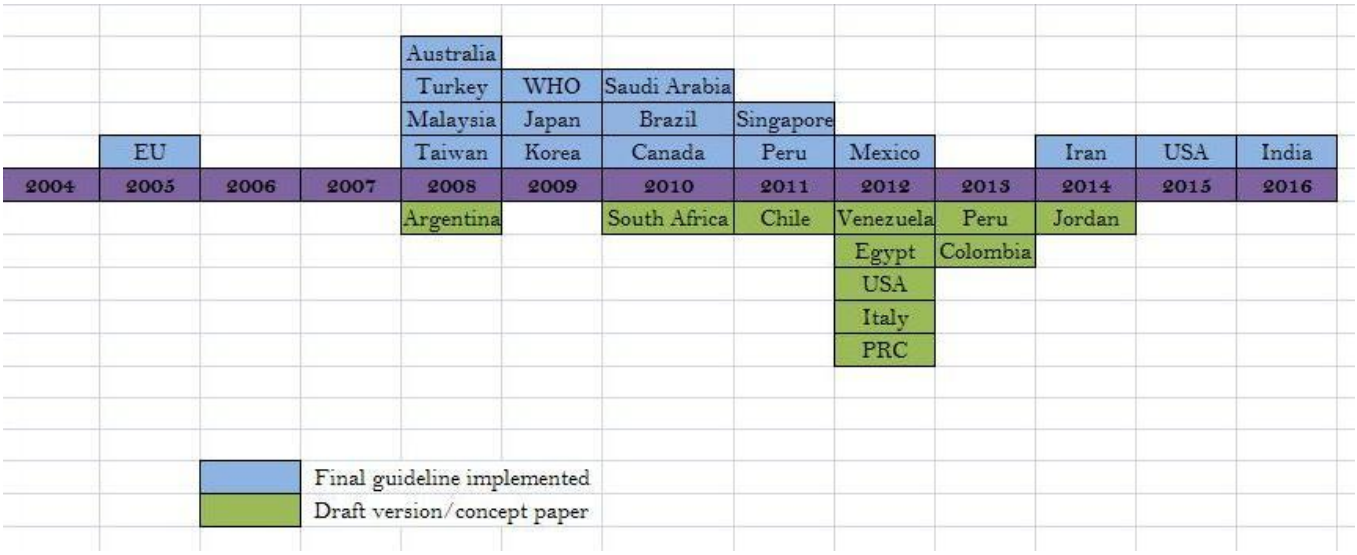

Figure 2.1 Evolutionary Scale of Regulatory Guidelines for Biosimilars from 2004 to 2016 (Adapted from Krishnan, Mody et al. 2015)

2.2 Manufacture of Biologics and Biosimilars

Unlike traditional chemical synthesis, the production of a biologic product from a living system does not follow an exact science as chemistry. Manufacturing biologics and biosimilars requires the design of complex multistep processes where mammalian and microbial cell cultures are utilized to manufacture therapeutic proteins. "The process is the product" is a long existing paradigm of the biological manufacturing process, implying that any changes in the process could significantly alter the product's safety and efficacy profile. Current biologic manufacturing facilities combine both analytical and process development methods to assess the scale up of the process with the aim of obtaining adequate productivity of a quality product. Once the biologic has demonstrated sufficient safety and efficacy (Appendix A13), it is then proceeded on to receiving regulatory agency and business feedback, before reaching final

approval and licensing. The steps in the preparation of a typical microbial cell culture are shown in Figure 2.2 below.

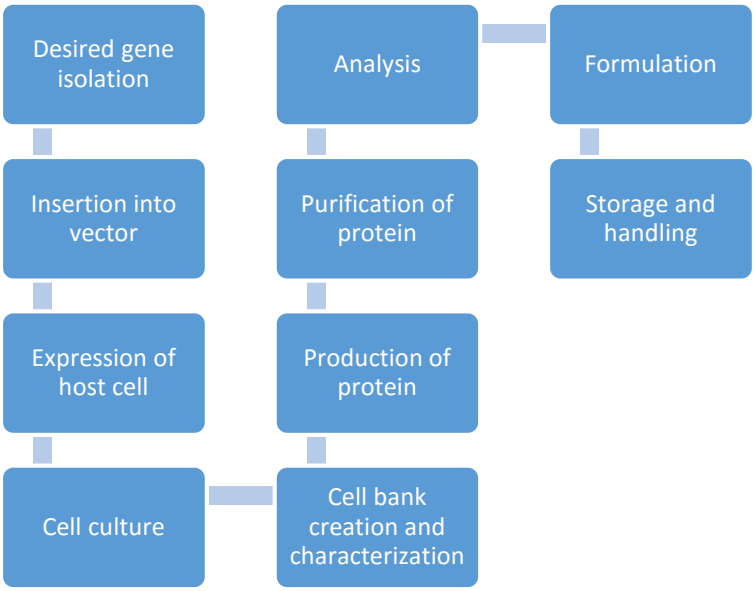

Figure 2.2 Typical Manufacturing Process of a Biologic Product (Sekhon and Saluja 2011)

Due to the sensitivity of the process, impurities need to be constantly checked for and removed from the process. Key contaminants include impurities in the host cell protein, cell debris, DNA and aggregates. Other parameters also need to be closely monitored and maintained, such as pH, flow rate, temperature, purity and media. Manufacturers are required to maintain clean equipment and regulatory approved manufacturing methods (Funding, 2016).

The manufacture and testing of biological therapeutics have strong approved industry standards and manufacturers may tailor these standards to meet the specifications of the protein. This includes developing individualized manufacturing methods, cell cultures, tests for release and other specifications. In the context of biosimilars, these tests include a comparative analysis between the biosimilar and originator product to identify any degree of variation between the two. The manufacturing process therefore needs to be carefully designed and closely monitored. This process comprises of selecting the appropriate originator biologic agent, detecting its critical molecular characteristics and tailoring the process to match these traits.

The manufacturing process is concluded by preclinical and clinical evaluation (Danese, Bonovas, & Peyrin-Biroulet, 2016). The entire process is described in Figure 2.3 below.

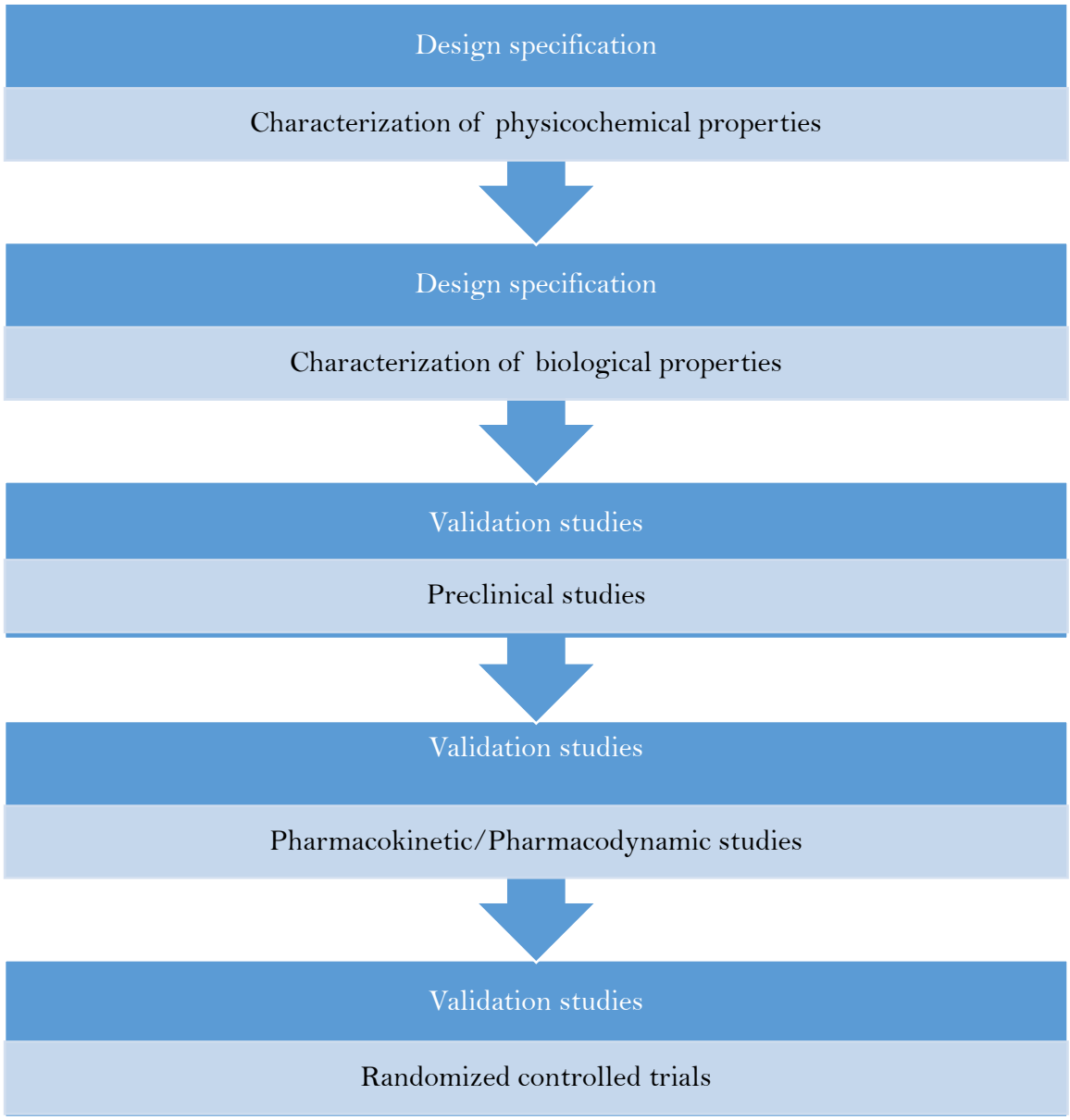

Figure 2.3 Outline of the Manufacturing Process of Biologic Drugs (Adapted from Danese, Bonovas, & Peyrin-Biroulet, 2016)

Since up to date manufacturing standards and tests are required to be used by the biosimilar sponsor, and the studies are compared with data from already commercialized reference products, reference of the products biologic license application does not need to be accessed by regulatory bodies to assess the biosimilar (AAM, 2013). However, engineering of the

process has to be done in the very early development stages within a narrow time frame and less certainty of success in order to commercialize the product as quickly as possible. Designing of a new process to replace an old one is highly costly and time consuming, making it tedious to scale up or scale down the manufacture of the biologic or biosimilar (Funding 2016). Manufacturers are often left to deal with the complex choice between having equipment sit idle or facing a supply shortage when redesigning a process to obtain a different volume of product.

It requires selection of an appropriate reference biologic agent, understanding of the key molecular attributes of the reference product, development of a manufacturing process to match these attributes, and finally preclinical and clinical evaluation.

2.3 Naming of Biologics and Biosimilars

It is essential that biological drugs as well as products approved as biosimilars be definitely identified and named to promote precision in writing and prescription filling. Healthcare professionals need to be adequately educated in providing complete product names and accurate batch numbers to biosimilar medication to facilitate pharmacovigilance. While generic small molecule drugs tend to have the same names based on their active ingredients, naming of biologics and biosimilars consists of identifying the variations in an already established product for which it can be identified as a new biotherapeutic with the requirement of a different name from the originator. The conflict in naming arises when many users judge a biosimilar as a “new” product due to its distinct formulation, altered processing, varied trade name or manufacturing company. Other users may deem the biosimilar product as similar enough to retain the same name, especially after their clinical comparability to the reference product has been established (Rader, 2011). Since biosimilars are not identical copies of the reference biologic, there is a necessity for healthcare providers to specify if certain biosimilars will be deemed as the drug of preference or whether therapeutic interchangeability protocols will be allowed for biosimilars that have been approved as interchangeable (Kim, 2015). The naming of biosimilars has been a bone of contention due to various innovator organizations preferring different INNs for biosimilars opposed to their brand counterparts. Individual regulatory regions tend to introduce their own biosimilar nomenclature schemes, while certain countries may conform to the regulation introduced by another region. In Australia, the INN of a biosimilar ends with the suffix “sim” (indicating the word “similar”) after which it is followed with any letters the manufacturer of the product decides on. Japan follows a nomenclature

system where the biosimilar INN is followed by the words "follow on" and the brand name having the letters "BS" incorporated into it (Robertson, 2015). In 2017, the US FDA introduced a regulatory framework where the INN of a biosimilar should consist of a "core name" succeeded by a four letter suffix. Normally, the USAN Council name is accepted for the reference product (USFDA, 2017). The World Health Organization's final proposal for a biosimilar nomenclature scheme revealed in 2016 closely resembles the prior version of the FDA's naming plan (addition of four random consonants as a suffix to the INN). The new proposal calls for the incorporation of a "biologic qualifier" (BQ) comprising of four random consonants as well as a non-mandatory two-digit checksum succeeding the INN of each biologic and biosimilar (Royzman, 2016). Below Table 2.1 is a list of biosimilars having the same INNs as that of their reference products.

Table 2.1 Biosimilars having shared INNs (Ramachandra 2014)

Brand Name	INN	Use	Manufacturer	Approval year
Avonex®	Interferon Beta-1A	Treats multiple sclerosis	Biogen	1996
Rebif®			Serono inc.	2002
Betaseron®	Interferon Beta-1B	Treats multiple sclerosis	Bayer Healthcare	1993
Extavia®			Novartis	2009
Asellacrin™	Somatropin	Growth hormone	EMD Serono	1976
Crescormon®			Genentech	1979

Accretropin™	Somatropin Recombinant	Growth hormone	Cangene	2008
Bio-Tropin®			Ferring	1995
Genotropin®			Pharmacia and Upjohn	1995
Humatrope®			Eli Lilly	1987
Norditropin®			Novo Nordisk	2000
Nutropin®			Genentech	1993
Omnitrope®		Growth hormone	Sandoz	2006
Saizen®			EMD Sereno	1996
Serostim®			EMD Sereno	1996
Tev-Tropin®			Ferring	1995
Valtropin®			LG Life	2007
Zorbitive®			EMD Serono	2003

2.4 Packaging of Biologics and Biosimilars

The packaging of biologics and their bio-generics pose several challenges to manufacturers due to their use of living organisms, a major factor which contributes to stability issues associated with such drugs (Hunt, 2015). Proteins tend to be sensitive to metal ions (such as manganese, zinc, barium and iron), and this threat is pronounced by metals which leach from glass during steam sterilization (Appendix A14). Furthermore, tungsten oxide utilized in the glass syringe needle insertion method can induce protein aggregation and subsequent degradation of the drug. The packaging process is delicate, with the need to ensure that there are no organic extractable species (such as those found in polymers) or metals (such as those found in plastics and rubber) which are leached from the packaging materials (Jeannin, 2017). These substances can significantly affect protein conformation and degradation, as well as present certain toxicity. Compatibility testing is essential to assess the safety and quality of the product before commercialization.

2.5 Labelling of Biologics and Biosimilars

Labels on medicinal products are another important source of information that requires regulation in the case of biologics and biosimilars. This information is usually presented in the patient leaflet, product characteristics and the label on the outer product packaging (GaBi, 2017). Though it does not recapitulate the development and assessment history of the product, it provides information to clinicians, pharmacists and patients with regard to the safe and effective use of the medication (Schwarzenberger, 2016). Appropriate labelling of biosimilars may allow for greater transparency, since the clinical data would be useful in enabling the physician in making a more informed decision on which product is best for the patient. Manufacturers strive to ensure that their biosimilar label is useful, fair and informative in terms of purpose. In 2016, the US FDA released a draft stating the requirement for biosimilar labelling to include a description of the clinical data corroborating the safety and efficacy of the originator product (USFDA, 2016). The European Medicines Agency (EMA) follows a more science based conceptual approach for biosimilar labelling, requiring the biosimilar label to be identical to theone utilized by the reference product (Schwarzenberger, 2016).

2.6 Pricing of Biologics and Biosimilars

Biologics fall into the category of high costing pharmaceuticals, promoting issues that require to be addressed with regard to controlling healthcare costs and accessibility of the drugs to patients. While certain guidelines promote competition and incentives for new drug pioneering (such as the BPCI), there is still a need to push prices down, such as that being accomplished by generics which have often taken the place of expensive branded drugs over the past years.

The introduction of biosimilars has signaled highly potential cost savings for patients requiring treatment by biologics, due to their lack of necessity for costly Phase I and II clinical trials as well as lengthy approval processes. Biosimilars possess a strong impact on the competition in the biologics market, predicting cost savings as much as $110 billion in Europe and the U.S by the year 2020 (Mortimer, White, & Frois, 2017). However, biosimilars are not perfect replacements for biologics, and still require expensive Phase III clinical trials (Appendix A15) and additional clinical studies before they can be introduced.

It has been seen that several factors such as manufacturing, development, pricing, clinician acceptance and barriers to entry have caused large differences in the development of the biosimilar market opposed to that of the generic market (Blackstone & Fuhr, 2013).Since biosimilars cannot be perfectly substituted with their originator biologics (as seen with generic and brand drugs), they enjoy more modest price discounts compared to that of generics. Furthermore, manufacturers of biologics close to patent expiry tend to raise the price of their product in order to boost revenues before they encounter biosimilar competition (Breese, 2016). An example of this can be seen in the pricing of Humira, which increased eight times in price between 2014 and 2016 (Rockoff, 2016). Studies show that brand name small molecule drugs tend to display over an average 75 percent fall in their sales after the introduction of their generic substitutes, while biologics tend to demonstrate a much more moderate price relief (Mortimer, White, & Frois, 2017). The biologic Neupogen lost only about 10 percent of its market share once its biosimilar competitor Zarxio was inaugurated into the market.

2.7 Immunogenicity of Biologics and Biosimilars

Due to their very nature, biologics and biosimilars are capable of setting off immune responses in the human body which may alter the safety or compromise the efficacy of the drug. Biologics

are complex proteins and have the ability to initiate a humoral or cellular immune response that can manifest in ways such as anaphylaxis (Appendix A16), infusion reactions, loss of clinical efficacy, change in pharmacokinetics (Appendix A17), hypersensitivity (Appendix A18) or cross reaction with endogenous proteins (Sharma, 2015). This immunogenicity that has a potential to vary from that expressed by the reference product is influenced by various patient, disease and product related factors. Immune feedback may affect the properties of the drug by promoting immune complex formation, alteration in the rate of clearance of the drug and nullification of the therapeutic activity of the drug (Reinisch & Smolen, 2015). Patient related factors consist of variables such as genetic background, pre-existing immunity, immune status, dosing schedule and route of administration. On the other hand, product related elements such as the manufacturing process, stability and formulation may contribute to the likelihood of an immune response (EMA, 2015). Furthermore, certain stabilizing agents and storage media can increase the potential of immunogenicity of a product, particularly when integrated with temperatures which are set beyond specification and the product is roughly handled. Molecular modification processes such as protein oxidation and aggregation are also responsible for generating immunogenicity in the molecular structure. Identifying the root cause of the immune response is challenging, especially since several factors may interact to cause the problem (Scott, 2014). Animals which possess the gene that codes for human insulin, interferons (Appendix A19) or tissue plasminogen (Appendix A20) activators tend to be effective anticipators of immunogenicity within patients. One of the more frequently used models for the prediction of immunogenicity in biosimilars is the immune tolerance exhibiting transgenic (Appendix 21) mouse (Schellekens, 2004). Models such as these however require stronger quantitative validation in order to detect the subtle differences between the biosimilar and its reference drug. With the lack of forecasting ability of these models, clinical studies prove to be the more popular method for the establishment of biosimilar antibody induction.

2.8 Pharmacovigilance of Biologics and Biosimilars

Pharmacovigilance is an essential aspect in the post approval process for biologics and subsequently, biosimilars. This tends to be a challenge for such drugs since the concurrent use of multiple medications by biologics taking patients makes it difficult to compile and evaluate an accurate safety profile from patients. Prescribers are often faced with the challenge of maintaining an appropriate monitoring system for which biologics have been prescribed for the

patient undergoing therapy. The protein configuration of biologics and biosimilars also leave them vulnerable to molecular modifications in the body via a variation of biological pathways, making certain safety concerns associated with the drug only be detectable outside the timeframes of the controlled clinical trials carried out (Sharma, 2015). This strengthens the necessity for post approval safety monitoring and risk management of these drugs. Furthermore, the abbreviated licensure pathway of biosimilars places a bar on the amount of safety data available on the drugs. A strong pharmacovigilance strategy must compromise of safety specifications of the biologic or biosimilar drug, which summarizes its identified and potential risks as well as identifies any region where there is a lack of sufficient information on the drug. These safety concerns should be addressed through well-defined activities and proposed actions with the added requirement of evaluation of potential for medication errors. Strict pharmacovigilance techniques are also necessary to identify potential variation points in safety between biosimilars and their corresponding reference biologics. Risk management strategies should be made available in the plan which should highlight the effectiveness of the proposed activities as well as provide additional information such as medication guide supplements and restriction of access (Reinisch & Smolen, 2015). The plan is designed to improve and expedite the biosimilar manufacturer's faculty to obtain safety information of the product.

2.9 Interchangeability of Biologics and Biosimilars

A biosimilar product can be considered interchangeable with its originator biologic if it is evaluated and approved to be capable of substitution with the reference product by a pharmacist (usually without the intervention of the prescriber of the originator product), including meeting additional standards beyond bio-similarity (Li, 2016). Interchanging or switching of medication addresses the medical practice of physician exchanging the product that a patient receives with another drug product targeting the same therapy. This switching is usually driven by a clinical imperative seeking an alternate suitable patient therapy due to issues such as efficacy or tolerability with the previous product (IFPMA, 2017). The U.S Food and Drug Administration identifies an interchangeable biosimilar as one that "can be expected to produce the same clinical result as the reference product in any given patient and, if the biological product is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between the use of the biological product and

the reference product is not greater than the risk of using the reference/ product without such alternation or switch" (USFDA, 2015). In order to be deemed interchangeable, the efficacy and safety risk of the biosimilar must not exceed the risk of utilizing the reference product without any substitution. This calls for stringent post marketing information on the biosimilar and crossover studies to determine its homogeneity with the reference product (Blackstone and Fuhr, 2012). Interchangeability between biologics and biosimilars is not readily accepted in several countries for a number of arguments including the doubt of value between the brand name biologic and generic drug, the concern over the authenticity of the biosimilars performance with regard to its differences from the biologic, lack of differentiated regulations on the reference product, the biosimilar and their interchangeability as well as the lack of information available to the consumer (Cassels, 2017). There are several considerations which need to be accounted for when interchanging biological drug therapy with a biosimilar one. It is necessary to evaluate these factors in the perspective of the patient, disease and product related factors. Potential risk factors have been summarized in Table 2.2 below.

Table 2.2 Risks and Considerations in Interchangeability (Associations 2017)

Potential Risk Factor	Considerations	Sources of evidence
Risk of product not being approved as per standards in global guidelines supporting biosimilar development	Has the biosimilar been approved according to the principles outlined in the WHO Similar Biotherapeutic Product (SBP) guidance? The presence of "non- comparable biologics" (NCBs) in certain parts of the world implies the existence of drugs that have not been directly compared with the reference product and therefore may not meet global standards. Switching scenarios between these types of products and their reference product represent	Approved by Regulatory Authorities in accordance to WHO guidelines on Similar Biotherapeutic Products (SBPs)

	the highest level of uncertainty and risk to patient safety	
Switching between the reference product and its biosimilar	Regulatory submissions for a biosimilar may sometimes consist of information on substituting the reference product for the biosimilar and/or vice versa. The quantity and type of this information will differ with each submission.	For example, public assessment reports from Regulatory Authorities & scientific literature
Switching between biosimilars	It is less likely for there to be any clinical data directly comparing different biosimilars to the same reference biologic in the similar group of related products. This is not a mandate in regulatory filings. Switching between biosimilars represents an unknown, and one that harbours considerable uncertainty.	There may be anecdotal or real world data available
Nature of the product	All biologics display a degree of immunogenicity, however, the nature and consequences of immunogenicity differ based on the product. Information on the reference product and the biosimilar products may be of great	For example, public evaluation reports from the related regulatory authorities and scientific literature

	assistance in this aspect. For biological products that are substitutes for a naturally-occurring hormone/cytokine/receptor, there is an increased risk of serious consequences, (e.g. if antibodies directed towards native proteins are produced).	
Route of administration and dosing device	Subcutaneous administration shows a greater degree of immunogenicity compared to intravenous administration. Usage of a different dosing device for the biosimilar may potentially increase the uncertainty as patients may be not be sufficiently familiar, when administering the product.	Adequate labelling for biosimilar and reference products possessing proper dosing instructions
Extent and scope of post approval safety data	Where stringent systems for post approval safety monitoring of biologics including biosimilars exist, i.e. in jurisdictions compliant with WHO guidelines, such data may provide reassurance that the real-world use of the product does not result in any unexpected risks.	Design and assessment of a risk management plan or evaluation of post marketing safety reports from related regulatory authorities. Overview of publications possessing review of safety data

3. Non Comparable Biologics (NCBs)

Biosimilars tend to often be confused with non-comparable biotherapeutic products (also termed as "biomimics" (Castañeda-Hernández, González-Ramírez et al. 2015)). These non-comparable biologics (NCBs) are copies of reference biologics which have not undergone the strict evaluations and regulatory requirements as undergone by biosimilar products, under standards set by WHO, EMA, USFDA and other regulatory bodies, to meet biosimilarity (Mysler, Pineda et al. 2016). The approval of these products is ambiguous since they lack data from comparative studies with the reference product. These products possess limited analytical evidence and clinical trial data, making it difficult to sufficiently compare their safety and efficacy profile with the licensed reference biologic. In certain countries with less stringent drug regulatory pathways, these NCBs are often marketed without clinical trials or sufficient disclosure of data to disclose their degree of biosimilarity, and are considered as biosimilars (Álvarez, Mysler et al. 2014). As a result, there is a reduction in the market exclusivity of innovative biotherapeutic products and an increase in risk to the integrity of patient therapy. This calls for a well-defined and transparent regulatory framework to properly distinguish between NCBs and biosimilars by regulating their development, approval and post authorization criteria (Roche, 2017).

4. Current status of the Bangladesh Pharmaceutical Industry

Bangladesh holds a prominent position as a pharmaceutical manufacturer in South Asia, meeting both domestic and international demand. Similar to most other countries in the region such as Pakistan and India, it possesses well-structured regulatory pathways for the approval of pharmaceuticals (Kalra, Khan et al. 2016). Under current national policy, raw materials locally manufactured are protected by restrictions on their import unless adequate quantity of the material is present within the local industry. Multinational companies (MNCs) are also not allowed to market their products nationally without the setup of their own factories within the country. The marketing of foreign brands are also prohibited if there is the presence of at least three identical or similar products being locally produced. The pharmaceutical industry in Bangladesh benefits from the Trade-Related Aspects of Intellectual Property Rights (TRIPS) waiver on pharmaceutical products for developing nations. However, this waiver is set to expire in 2033(WHO 2015). In order to sustain growth after 2033, the industry must innovate and identify new opportunities. As of now, although the country meets about 98 percent of its local pharmaceutical demand (Durjoy 2017), it still relies on foreign imports for costly biotherapeutic products. With the patent expiration of most first-generation biologicals internationally in 2004, and new biologics having a patent period of just twenty years (Blackstone and Fuhr 2013),prospects for developing biosimilars are brighter than ever.

4.1 The Adoption of Pharmaceutical Biotechnology in the Pharmaceutical Industry of Bangladesh

Although in its initial stages, the pharmaceutical industry of Bangladesh has initiated the utilization of biotechnology in the field of medicine with the aim of meeting global pharma trends and reducing the local demand for biotechnology developed products. As a result, pharmaceutical companies are investing huge capital behind the development of anti-cancer, anti-HIV/AIDS, vaccines, insulin and several other biodrugs to meet local demand. Some of the companies which manufacture anti-cancer drugs in Bangladesh include Beacon, Techno Drugs, Beximco and Incepta while Roche (Bangladesh) and Sanofi- Aventis (Bangladesh) are renowned marketers of imported anti-cancer drugs. Novo Nordisk (Denmark) is currently the frontliner in marketing human insulin while Glaxo-SmithKline (GSK) and Sanofi-Aventis (Bangladesh) are popular marketers of vaccines within the country. Current trends of pharmaceutical companies include importing the basic raw materials before manufacturing the

finished biotech products. The high amount of technology, expenditure, time consumption, etc. of biosimilar development from scratch makes it a challenge for companies to take up such operations without any aid from the government or foreign investments. An intelligible policy targeting to solve the shortcomings in infrastructure and funding could significantly facilitate biotechnological research. Similar to the API Park which is being developed within the country, the government should take steps to install its own "Biotech Park" and "Genome Valley" similar to those established in India. Furthermore, collaboration between industries and universities having their own lab facilities should be encouraged in order to promote research into the development of biotech molecules.

4.2 Landscape of Current Regulatory Guidelines

In order to obtain a better understanding of the presiding regulatory guidelines governing biosimilars within the country, data was collected from the reigning drug regulatory authority, the Directorate General of Drug Administration (DGDA). Under current principles, the definition of biosimilars is dictated by that set by the WHO biosimilar guidelines – "A biotherapeutic product which is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product". The DGDA has a unified drug policy for all activities related to the production, procurement, import, export, marketing and pricing of all kinds of medicines. This drug policy is updated each year and incorporates information from the Drug Act 1940, Drug (Control) Ordinance 1982 and Drug Rules 1946. The current decree maintains the need to approve drugs within the country only after they have received prior approval from the drug regulatory authorities of seven other countries (UK, USA, Germany, Japan, Australia, Switzerland and France). Drugs approved for distribution and use have to be acceptable under pre-existing standards set by the US FDA, UK Medicines and Healthcare Products Regulatory Agency (MHRA) and the British National Formulary (BNF). This significantly strengthens the drug laws binding to products manufactured and utilized within the country but falls short with respect to the need for individualized treatment to each branch of drugs. The regulatory guidelines for biologics are incorporated as sub sections within the same drug policy, and do not have their own individual rules and regulations with regard to their unique parameters from other drugs. These rules are also not as regularly updated as those in foreign countries with reputable drug regulatory authorities. The current policy states the need for the maintenance of GMP in the manufacture of biologics and biosimilars, but does not specify any particular GMP standards to be followed. Rather, the standards are set based on

each manufacturing company's production capacity, technology available and storage capability. The approval process for bioproducts such as vaccines are currently handled by three expert committees, namely the CMC (Chemistry, Manufacturing and Controls) committee, the Clinical trial document evaluation body and the legal system utilized for all drugs within the policy. Approval is also directed by the Drug Control Committee and technical sub committees. The DGDA maintains data on the indications, toxicology levels, pharmacodynamics (Appendix 22), pharmacokinetics, pre-clinical studies on each and every drug, setting stringent standards and maintaining an equally lengthy registration procedure for biosimilars as that of biologics. This harmonizes the challenges faced with the introduction of biosimilars to those faced with biologics or generic drugs, due to the indiscriminate standards set for each drug within the policy. There is no separate naming and labelling system for biologics and biosimilars, labelling systems within the policy are differentiated more on the basis of dosage forms and the individual indications (Appendix 23), contraindications (Appendix 24) and side effects information on each drug. Although complete data profiles on the safety and efficacy of each drug are not provided to clinicians, the DGDA approves the provision of materials which provide conclusive data of each drug product as well as a strong risk benefit analyses. This information is ensured by the DGDA to be authentic and cater to any clinical queries the doctor may have with regard to the therapeutic capabilities of the drug. Under current guidelines, the DGDA promotes the operation and development of a pharmacovigilance system on biologics and other drug products with the aim of being able to monitor if drug products approved for use within hospitals of the country are having their desired effects and therapeutic outcomes. There are currently no regulatory boundaries set with regard to interchangeability issues of biologics and biosimilar drugs in the clinical setting, preferring the clinician to make an independent an informed decision on which drugs should be prescribed for treatment.

5. Methodology

The purpose of this report was to review the general status of biologics and biosimilars globally, and then to research the current scenario of biologicals in Bangladesh in order to establish a case for the introduction and propagation of biosimilars within its drug industry. This case will be built based on a current view of the presence of biologics and biosimilars within the drug market and eventually relate it to the availability and accessibility of these drugs to the people of Bangladesh highlighting the challenges involved in introducing, manufacturing and prescribing biosimilars within the present scenario.

Secondary data for the study was compiled from several biologics and biosimilar related journals endorsed by Nature, JAMA and other distinguished academia, relevant articles and guidelines. All the information collected were accurately referenced and compiled with the onus of providing a detailed understanding of biologics and biosimilars and their applications. Attempts were taken to identify any gaps or missing information within the literature.

Primary data was then obtained via the design and implementation of a questionnaire based survey. Three sets of questionnaires were made – each individually designed with questions targeting clinicians, industry experts and academicians presently employed within the city. We kept a target of 50 clinicians, 40 industry experts and 50 academicians. The questionnaires were tailored to answer several questions regarding the challenges and outcomes of biosimilar introduction and in demonstrating its feasibility in Bangladesh. The survey language was English and constituted of fifteen questions for clinicians, twenty five questions for industry experts and eleven questions for academicians. The questionnaires constituted of multiple choice questions, open ended questions and questions aimed at measuring each respondents' attitudes to the topic with the aid of Likert scales. Each of the three questionnaires were pre-tested before the final questionnaire for each was developed. For clinicians, the sampling frame included doctors practicing in hospitals within Dhaka city who are well versed on the applications and benefits of biosimilars and biologics, as referenced by the director of each hospital. Industry experts citywide were also approached based on recommendations from each individual industry Head. Academicians with experience in teaching courses or subjects with regard to biologics and biosimilars were targeted based on references or counsel provided by the Dean of the respective departments. All respondents were notified by prior email invitations and each respective administration was officially informed before the survey was conducted

within the premises. Data collected during the survey was kept authentic by constant supervision from the survey taker and none of the respondents were allowed access to secondary information resources during the course of the survey.

The information from both primary and secondary sources were compiled and scrutinized before being incorporated into the study. Data obtained from the questionnaires were analysed and interpreted to provide both quantitative and qualitative information.

While our study integrated intelligence on biosimilars from several reputed journals, there was a lack of documented and accessible data corresponding to the Bangladesh biosimilar industry. The data obtained from the questionnaires were also limited due to a lack of candidates who were available to provide input within the time frame of the survey. The research questions (RQ) and the related research objectives (RO) for this study were:

RQ1: What is the status quo of the Bangladesh biologic and biosimilar drug industry?

- RO1: Investigate whether there a clear concept of biosimilars among the clinicians, industry professionals and academicians.
- RO2: Investigate whether the concept of biosimilars feasible in our country in their opinions.
- RO3: Address the major challenges with the introduction of biosimilars in the drug industry.
- RO4: Determine if Bangladesh has the regulatory requirements for biologics and biosimilars clearly outlined.
- RO5: Determine if the fairly long development period of the biosimilar would be a disincentive in the further development of the Bangladesh drug industry under the present circumstances.
- RO6: Investigate if there is any imported biosimilar products in Bangladesh that are prescribed.
- RO7: Determine the main sources from which clinicians learn about biosimilars.
- RO8: Determine if doctors have the resources required for facilitating biosimilar programs.

RQ2: How can the introduction of biosimilars benefit the welfare of the people in Bangladesh?

- RO1: Identify the major drivers that would encourage doctors to endorse the prescribing of biosimilars.
- RO2: Identify factors that would encourage local doctors to prescribe biosimilars.
- RO3: Identify the advantages of a biosimilar.
- RO4: Determine if the quality profile of a biosimilar fall within the limits of the quality profile of the innovator biologic.
- RO5: Identify whether the process of obtaining license for a proposed biosimilar product is less tedious and time consuming than that needed to obtain the license of its reference product.
- RO6: Investigate if doctors would consider prescribing a biologic over a conventional small molecule drug, in a situation where treatment is possible.

RQ3: How can the adoption of biosimilars in the Bangladesh drug industry be facilitated?

- RO1: Identify an appropriate approval process for biosimilar drug products.
- RO2: Identify what the major changes in regulatory guidelines for new biosimilar drugs should be as opposed to those utilized for reference medicine.
- RO3: Investigate whether a biosimilar product and its reference biologic can be used interchangeably.
- RO4: Identify whether a proposed biosimilar product have a delivery device or container closure system different from its reference product.
- RO5: Determine what the labeling requirements for newly introduced biosimilar products should be and which guidelines they should follow.
- RO6: Determine if the proposed name for a newly introduced biosimilar product will be suitable and unambiguous to patients.
- RO7: Investigate how a manufacturer of biosimilars can demonstrate the reliability of his product, especially in terms of non-immunogenicity.
- RO8: Address whether it is important for manufacturers and prescribers to know and make available data about development process, clinical efficacy and safety.
- RO9: Identify be the best way to educate patients on the use of biosimilars.
- RO10: Investigate how the pricing of biosimilars should be strategized.
- RO11: Identify how the price of biosimilars should vary with that of the reference product.

- RO12: Identify the necessity of comparability studies in the determination of the effectiveness of biosimilar products with regard to their safety and efficacy.
- RO13: Determine if lower cost of the biosimilars should be prioritized over the maintenance of an identical quality profile to that of the reference product.
- RO14: Determine whether there should be separate pediatric assessments and programs for the approval of the administration of biosimilar medication in children.
- RO15: Identify whether leading universities incorporate course material on biologics/ biosimilars in their curriculum.

RQ4: Are Non-Comparable Biologics (NCBs) synonymous to biosimilars?

- Determine if there is a clear perception of Non-Comparable Biologics in industry experts within the country.

6. Results

Our survey data was analyzed and interpreted to obtain the following findings with regard to the research goals and objectives of the paper.

Research Question 1: What is the status quo of the Bangladesh biologic and biosimilar drug industry?

We first analysed the understanding of biosimilars among industry professionals and academicians, asking them to select a definition that reflects their concept of biosimilars. Answers were distributed according to Table 6.1.

Table 6.1 Understanding of Biosimilars among Industry Professionals and Academicians

	Industry Experts	**Academicians**
A biologic that demonstrates equivalence with the original biodrug and has all the preclinical and clinical trials equal to those already performed with the original biodrug	72%	54%
A biologic that demonstrates bioequivalence with an original biodrug and does not need clinical trials to be commercialized	11%	26%
A molecule equal to that of the original biodrug but of lower production cost	17%	11%
An attempt to copy an innovative biodrug and will never be equal to it	0	0

A generic biologic of an already commercialized biodrug	0	9%

Industry experts were then asked to give their opinion about the feasibility of biosimilar introduction in the nation's drug industry. The results are shown in Figure 6.1.

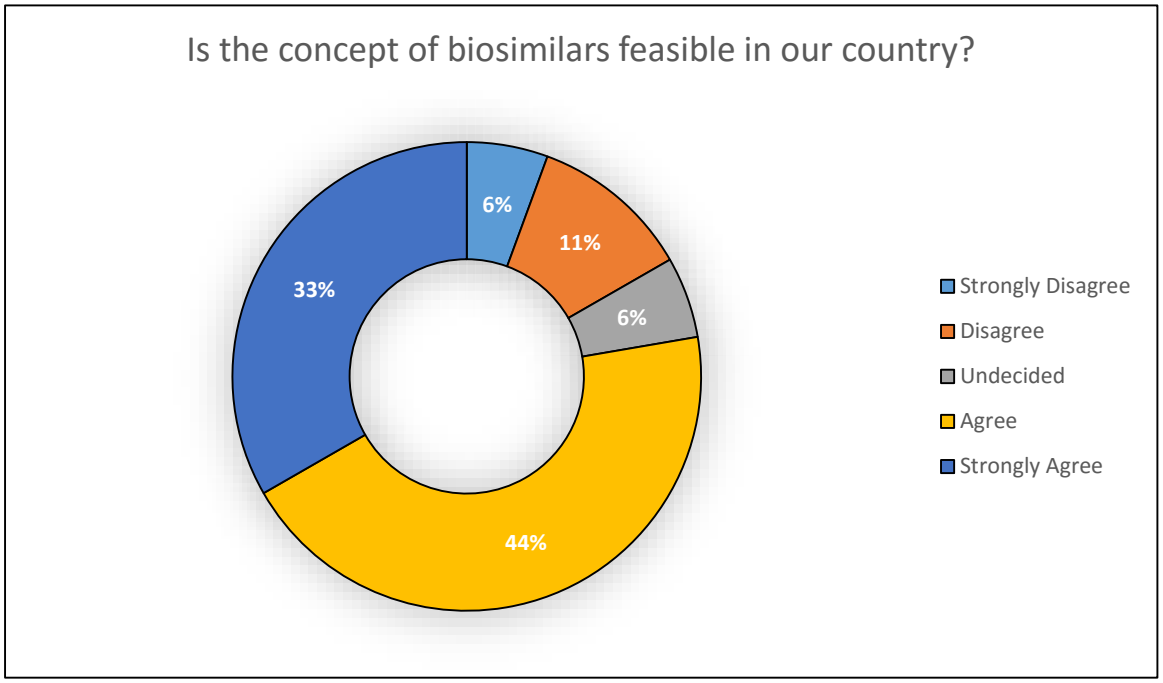

Figure 6.1 Opinion on the Feasibility of Biosimilars in Bangladesh by Industry Experts

Understanding the importance of clinician awareness on biosimilars, doctors from hospitals citywide were surveyed to investigate their degree of familiarity with this branch of drugs. Their responses were construed into the following Figure 6.2.

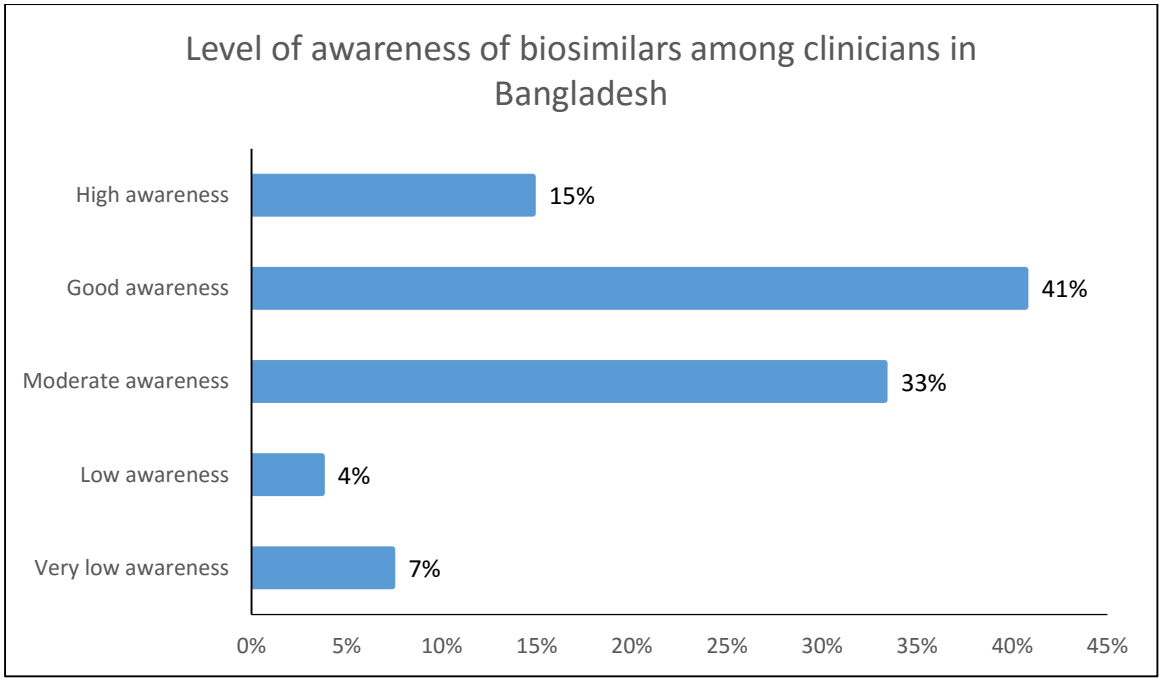

Figure 6.2 Level of awareness of Biosimilars among Clinicians in Bangladesh

The major challenges with the introduction of biosimilars in the drug industry, in the opinion of industry experts and academicians, were surveyed and the data generated is graphically presented in Figure 6.3.

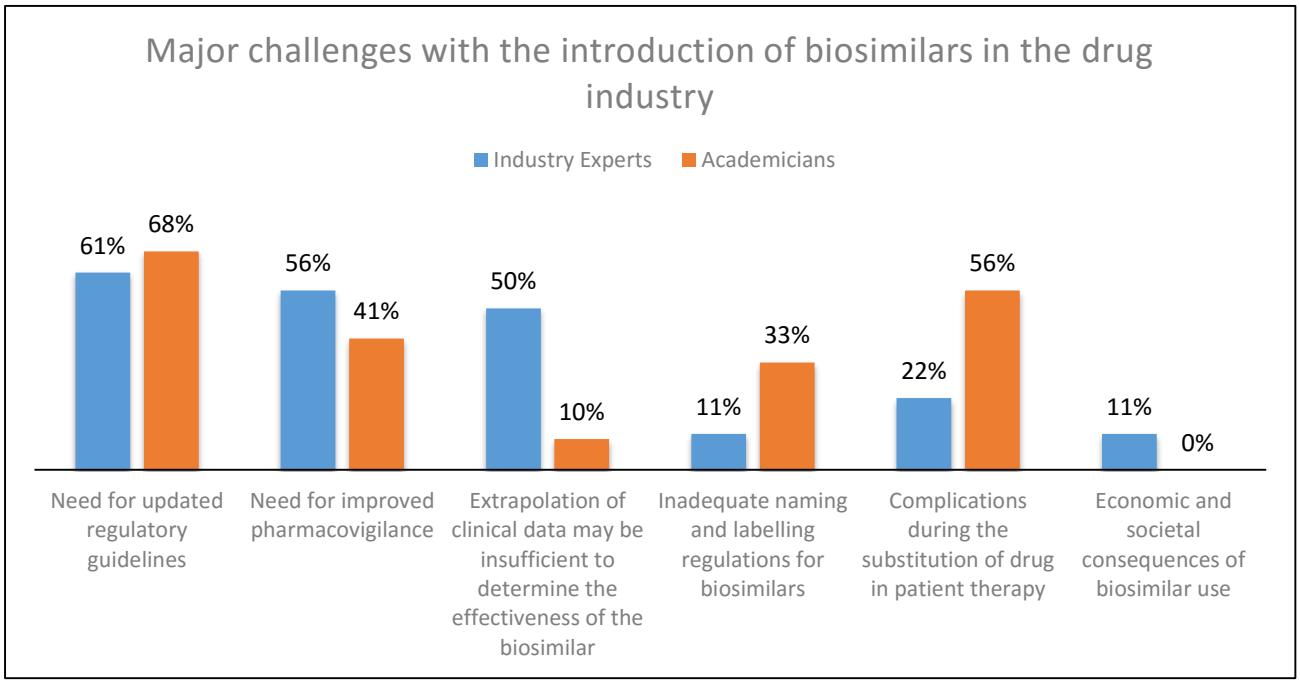

Figure 6.3 Major Challenges with the introduction of Biosimilars in the Drug Industry

With regard to regulatory criterion, industry experts were asked to state their opinion regarding

the clarity of biologic and biosimilar regulations in the current Bangladesh drug authority (DGDA) guidelines, upon which the following data is presented in Figure 6.4.

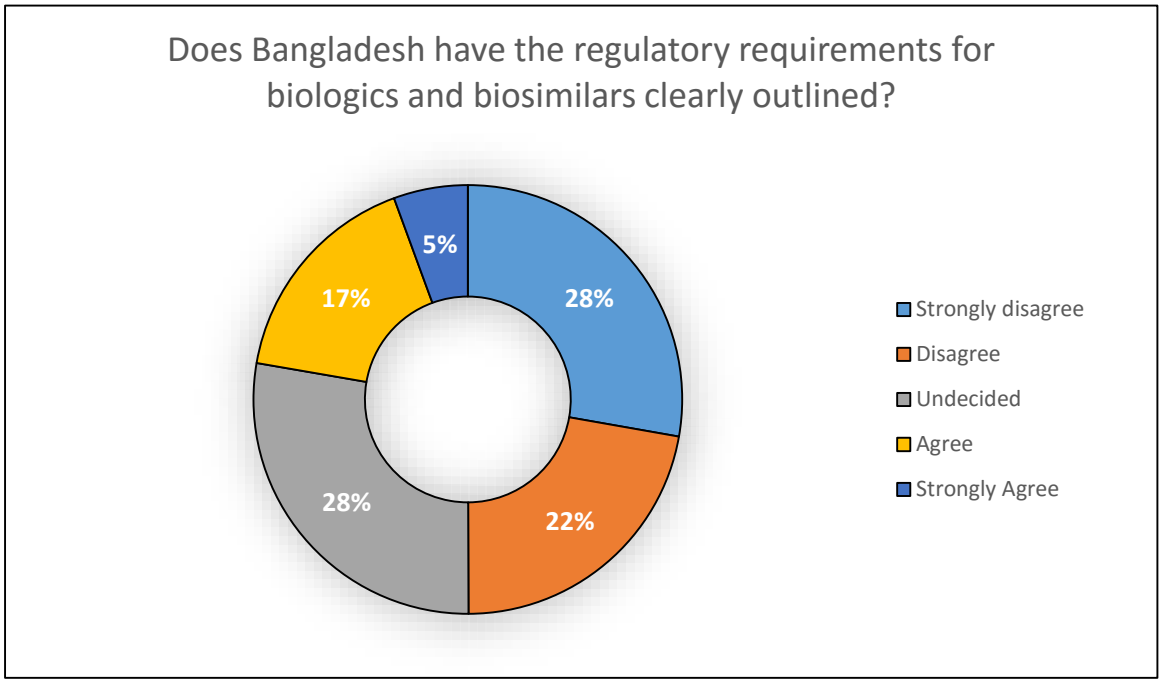

Figure 6.4 Strength of Biologics and Biosimilars Regulatory standards in Bangladesh

All three groups acknowledged that the benefit of a shorter application process for biosimilars was countered by a fairly long development period of the product. When asked if this was still a risk worth taking for further development of the Bangladesh drug industry under the present circumstances, responses from industry experts and academicians were obtained as shown in Figure 6.5.

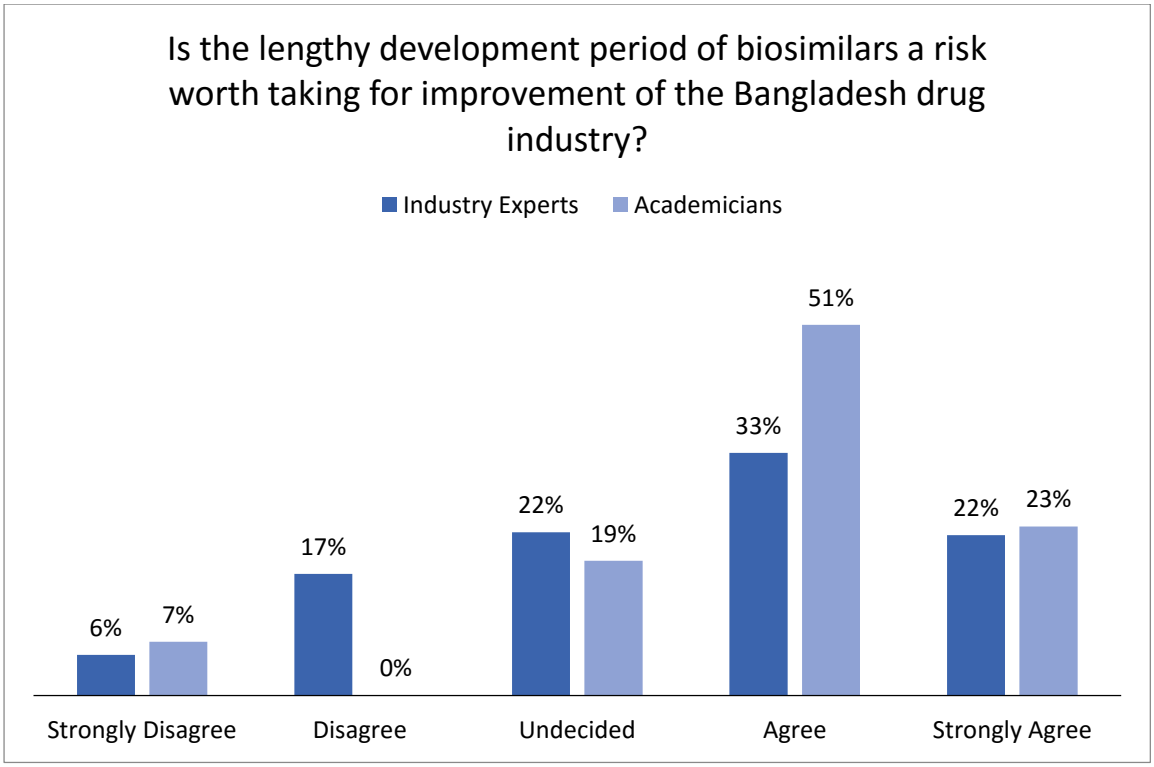

Figure 6.5 Risk-benefit analysis of the lengthy development period of Biosimilars

74 percent of clinicians vouched for the presence of imported biosimilars in Bangladesh for prescription, with most frequently mentioned examples being Filgrastim (brand name Neupogen), Trastuzumab (brand name Herceptin) and Rituximab (brand name Rituxin).

To investigate the sources of knowledge regarding biosimilars that mainly influence clinician practice, doctors operating in hospitals citywide were asked to pinpoint the main sources from which they had been made aware of the existence, applications and benefits of biosimilars. Their feedback was compiled and presented in Figure 6.6.

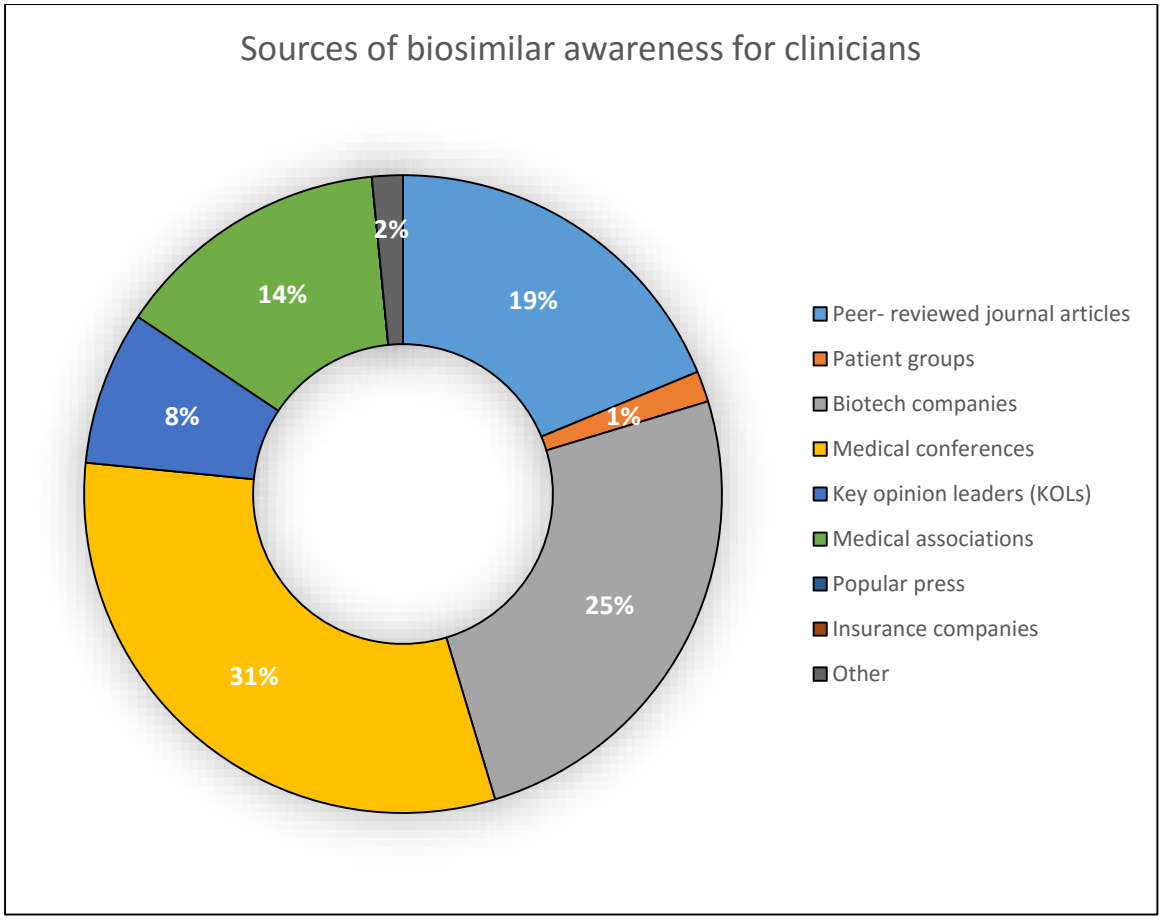

Figure 6.6 Sources of Biosimilar awareness for Clinicians in Bangladesh

Survey among clinicians recorded that **over 80 percent** of clinicians did not encourage the administration of biosimilar medication without sturdy special support programs for the patients undergoing treatment. However, **89 percent** of clinicians stated that they did not currently possess the resources required for facilitating such programs. Recommendations they had provided for arranging these resources include:

I) Doctor – patient counseling
II) Institutional seminar/symposium
III) Aid provided from biotech companies to raise awareness through use of leaflets and awareness programs
IV) Initiatives from government agencies
V) Aid provided from sponsors
VI) Joint venture projects organized by both public and private hospitals
VII) Training of nurses and other support staff

Research Question 2: How can the introduction of biosimilars benefit the welfare of the people in Bangladesh?

We first identified and compared the major drivers that would encourage general and local doctors to endorse the prescription of biosimilars. Industry experts were requested to select the reasons which would motivate doctors around the world to utilize biosimilars in their practice. Their feedback was construed and presented in Figure 6.7.

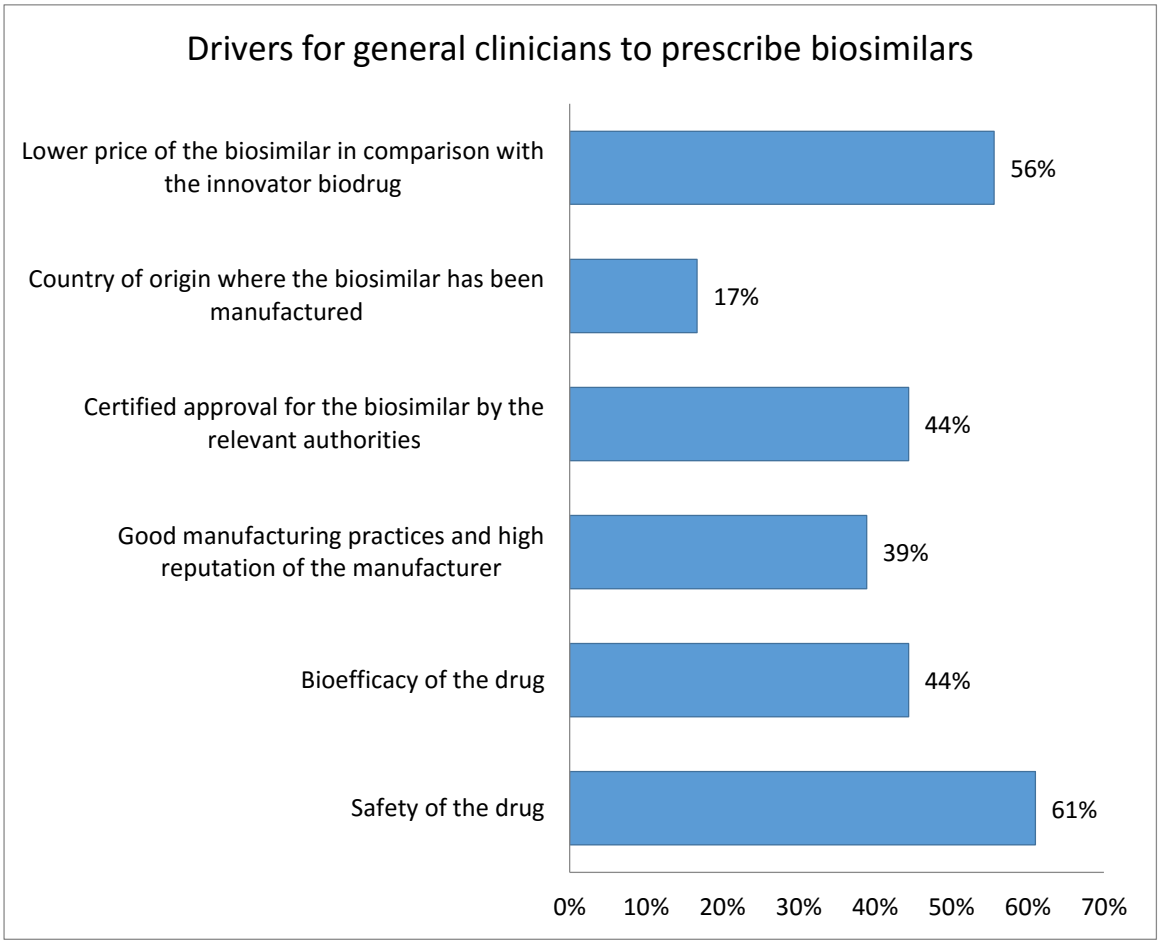

Figure 6.7 Drivers for general Clinicians to prescribe Biosimilars

We then investigated the factors which would spur local doctors within the city to prescribe biosimilars, taking input from both industry experts and clinicians. The data collected was analysed and presented in Figure 6.8.

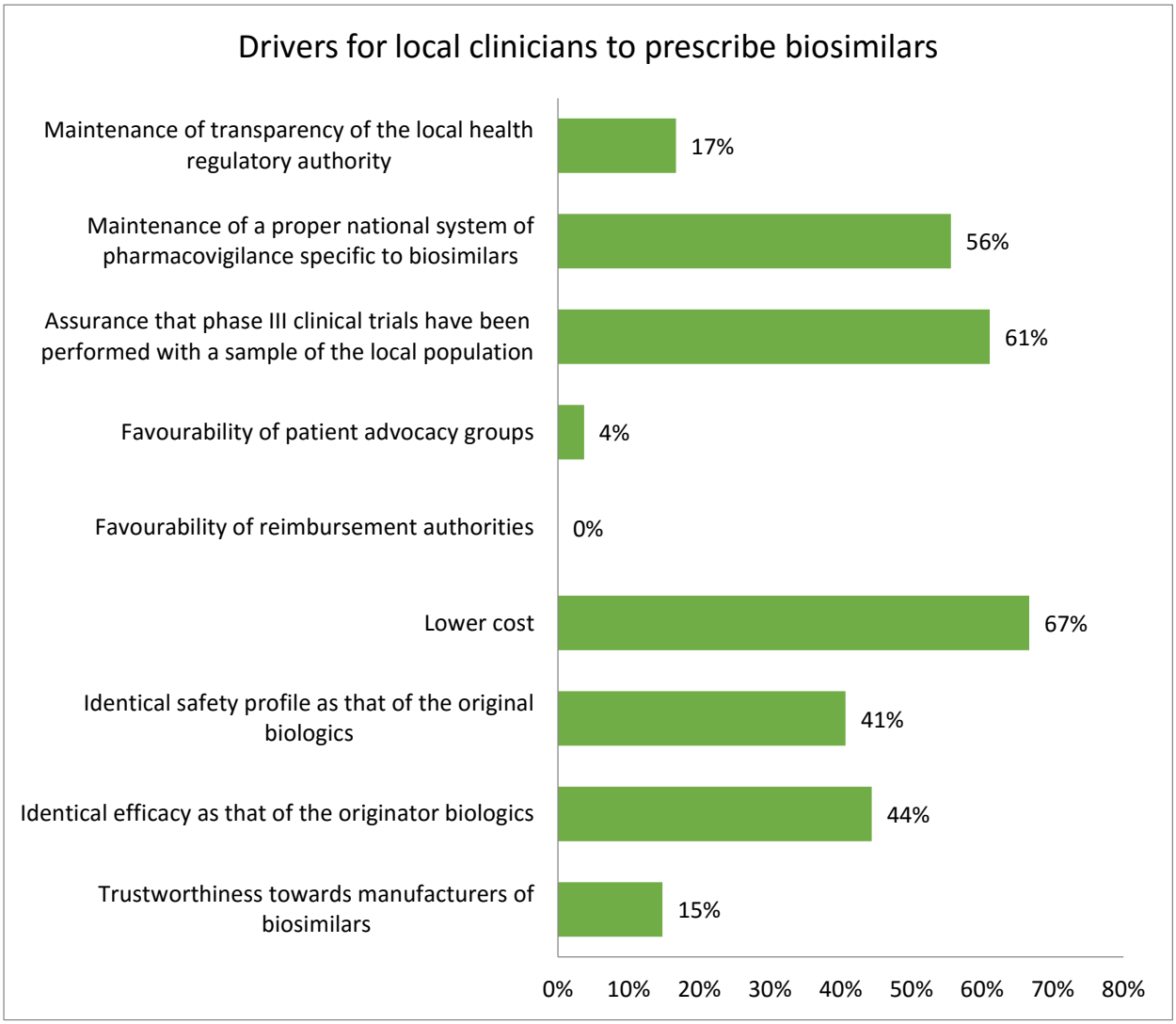

Figure 6.8 Drivers for local Clinicians to prescribe Biosimilars

With regard to the welfare of the people in Bangladesh and the rest of the world, industry experts and academicians were surveyed to obtain their opinions on the advantages of biosimilar medication. Their feedback was compiled and presented in Figure 6.9.

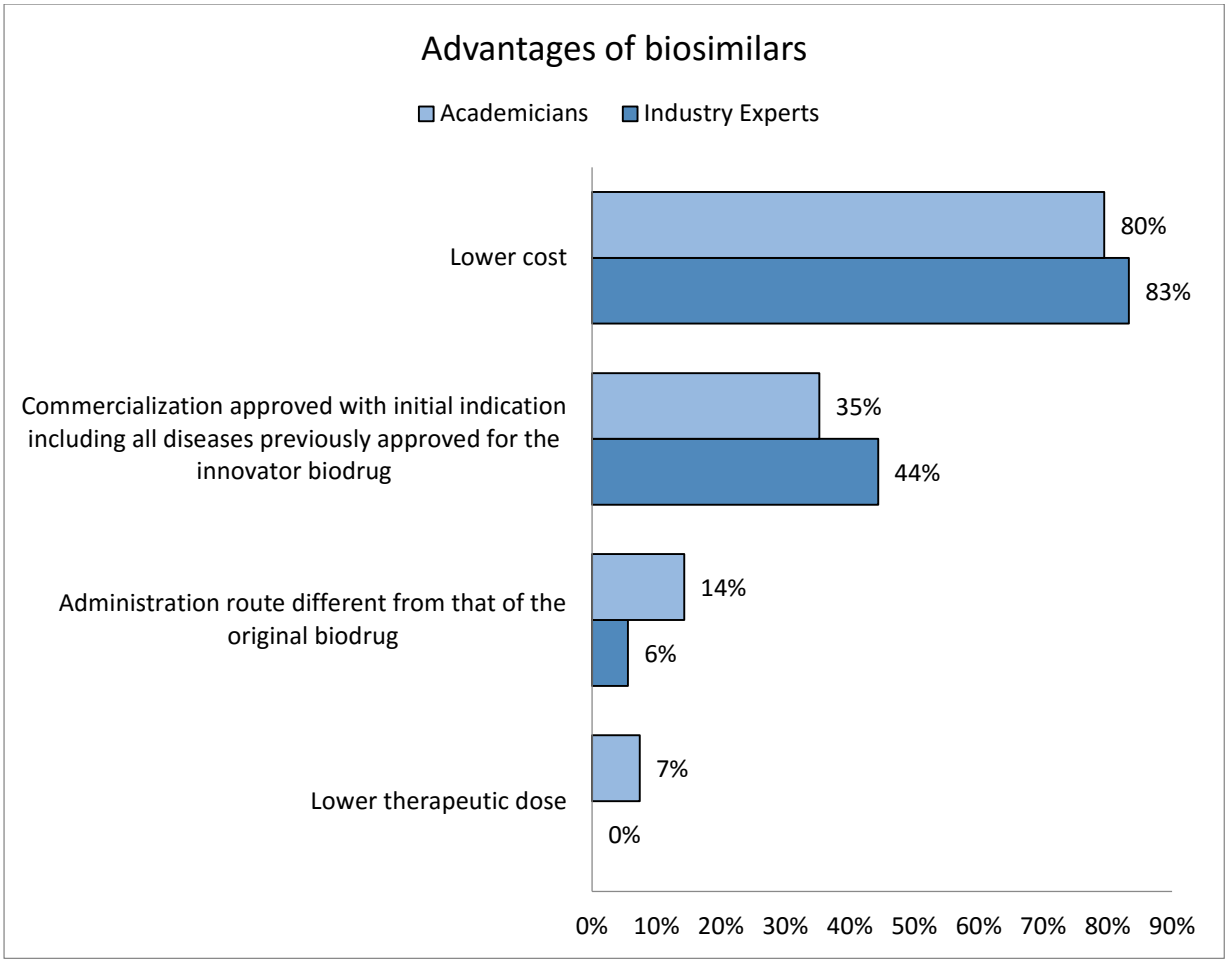

Figure 6.9 Advantages of Biosimilars

In order to justify the need for maintaining an identical quality profile of biosimilars with reference to the innovator biologic, we measured the attitudes of industry experts by asking them how much they agreed with the statement "The quality profile of a biosimilar should definitely fall within the limits of the quality profile of the innovator biologic, because one would expect that safety and efficacy will likely be similar too". Their responses were distributed in Figure 6.10.

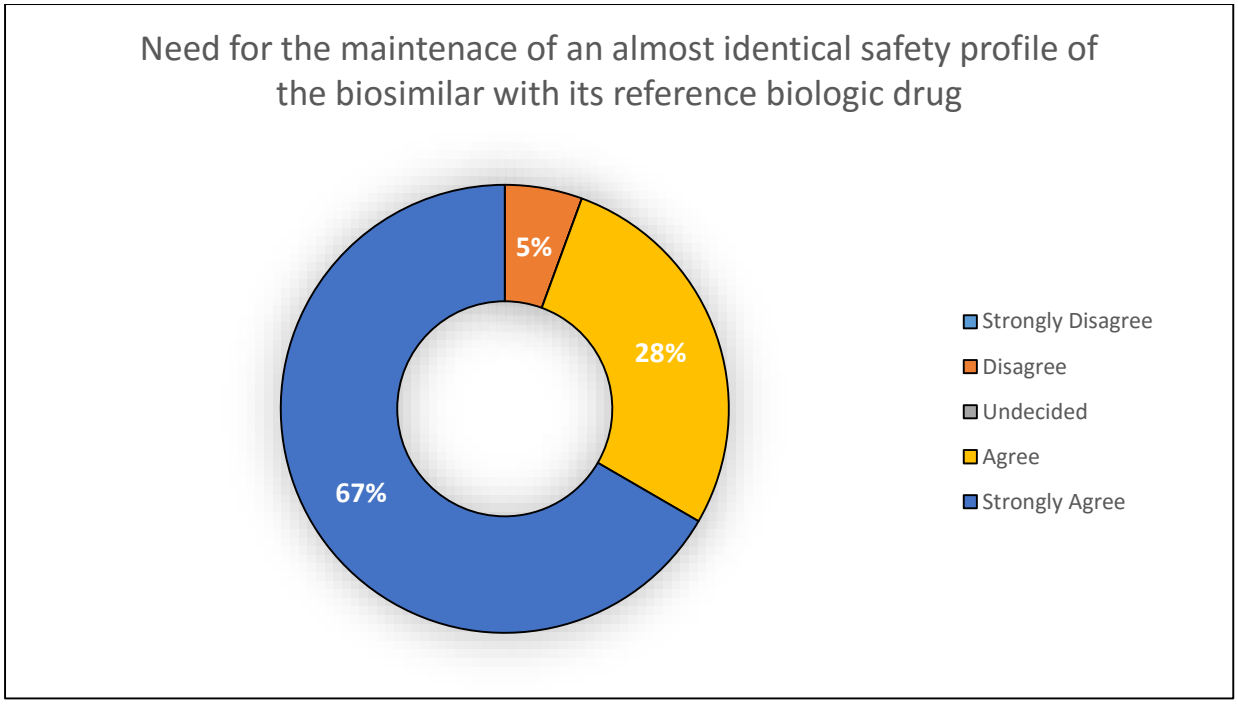

Figure 6.10 Necessity for identical Safety profile maintenance between Biosimilar and Reference Biologic

Industry experts were further requested to state their attitudes towards the license application process of biosimilars, with the hope that possession of a less tedious and time consuming process for biosimilar approval would aim in improving the degree of accessibility of the drug to patients. Their responses were distributed in Figure 6.11.

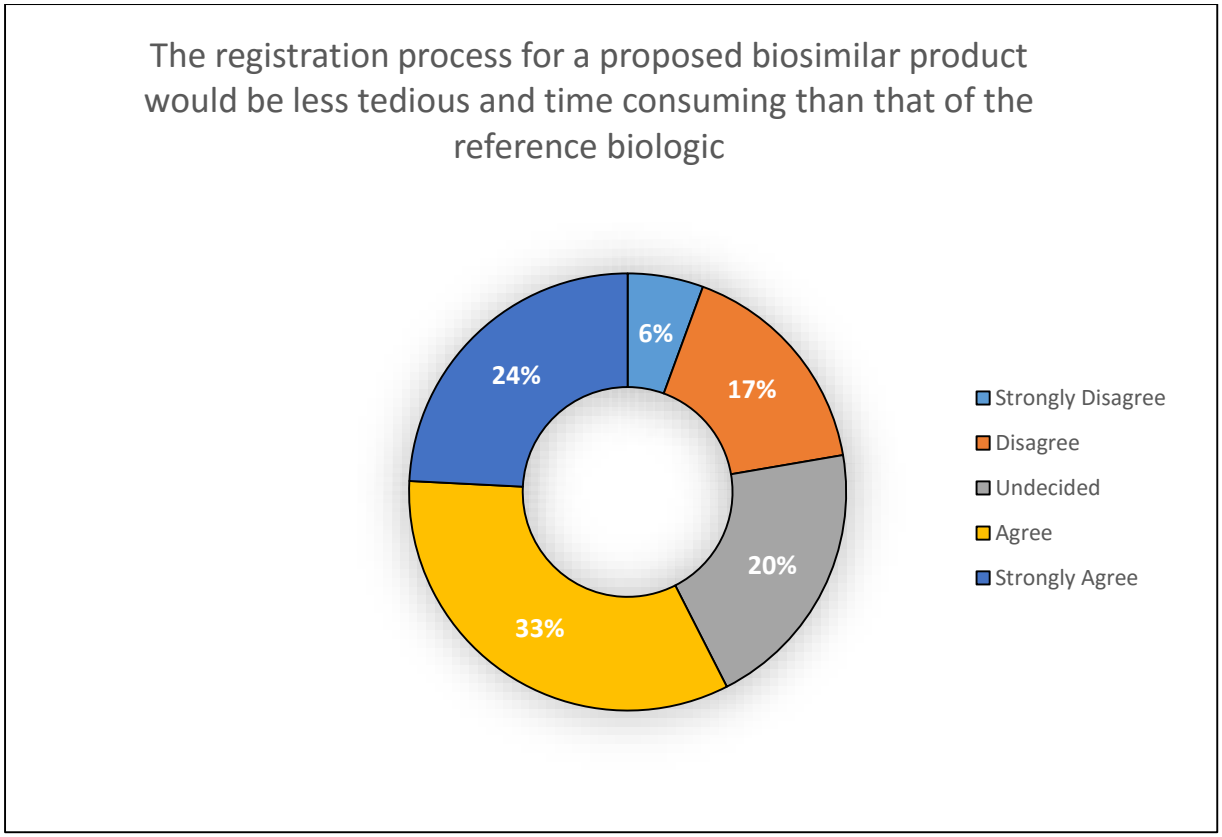

Figure 6.11 Comparison of the Registration process between Biologics and Biosimilars

The willingness of clinicians to prescribe biosimilars in the space where they were made completely available and accessible was then surveyed to obtain the Figure 6.12.

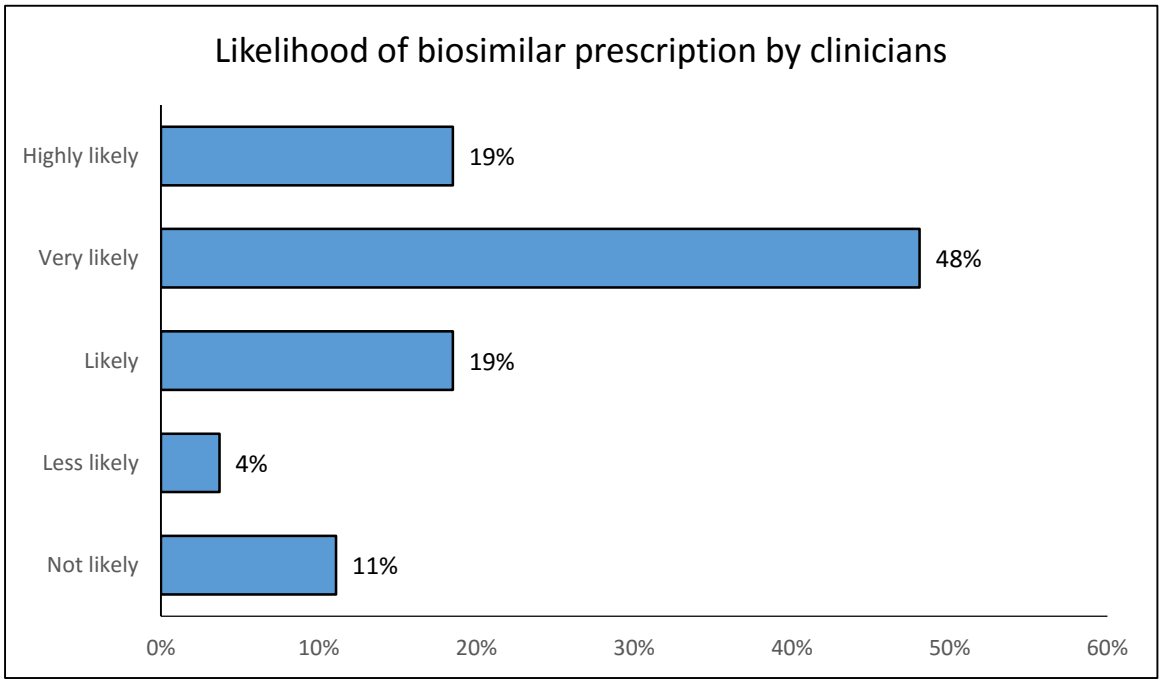

Figure 6.12 Likelihood of Biosimilar prescription by Clinicians

Research Question 3: How can the adoption of biosimilars in the Bangladesh drug industry be facilitated?

We first investigated current regulatory guidelines for biosimilar introduction and utilization. Understanding that there was a lack of stringent regulations in the current biosimilar approval process, we requested industry experts to provide feedback on an ideal approval process for biosimilars that could be operated within Bangladesh. Their proposals consisted of the following:

I) A biosimilar guideline endorsement designed by the DGDA with the help of WHO, EMA or other biosimilar guidelines from reference countries.
II) Monitoring and recording data of each biosimilar manufactured including its bioequivalence, innovator brand, country of origin, availability for local production and ensuring they are maintained within acceptable standards.
III) Requirement for manufacturers to submit complete clinical trial data (including that obtained from Phase III trials), carried out within their own facilities, to the drug regulatory authority before they can be approved.
IV) New biosimilars will undergo clinical trials with samples from the local population by approved R&D facilities with bioequivalent lab facilities before they can be commercialized.

67 percent of industry experts voted for the introduction of a different set of regulatory guidelines instilled for new biosimilar drugs opposed to those already used for the reference biologics, prodding the need for a new updated drug regulatory system within the country with regard to the use of such therapies. The following improvements to biosimilar regulatory guidelines were suggested for introduction:

I) Should be designed with a strong reference to WHO, EMA or suitable guidelines from other reference countries.
II) Should constitute of a regulatory system similar to that of small molecule generic drugs.
III) Individualized guidelines for each biologic and its corresponding biosimilar series.
IV) Addition of a separate dedicated pharmacovigilance monitoring section to the regulatory guidelines.

Interchangeability of the biosimilar product with its reference biologic would significantly improve the adoption of biosimilars within the national drug industry. Industry experts, clinicians and academicians were asked if biologics and their corresponding biosimilars could be freely utilized in place of each other during drug therapy, and if there were any patient risks involved with variability of the medication. Their feedback is presented in Figure 6.13.

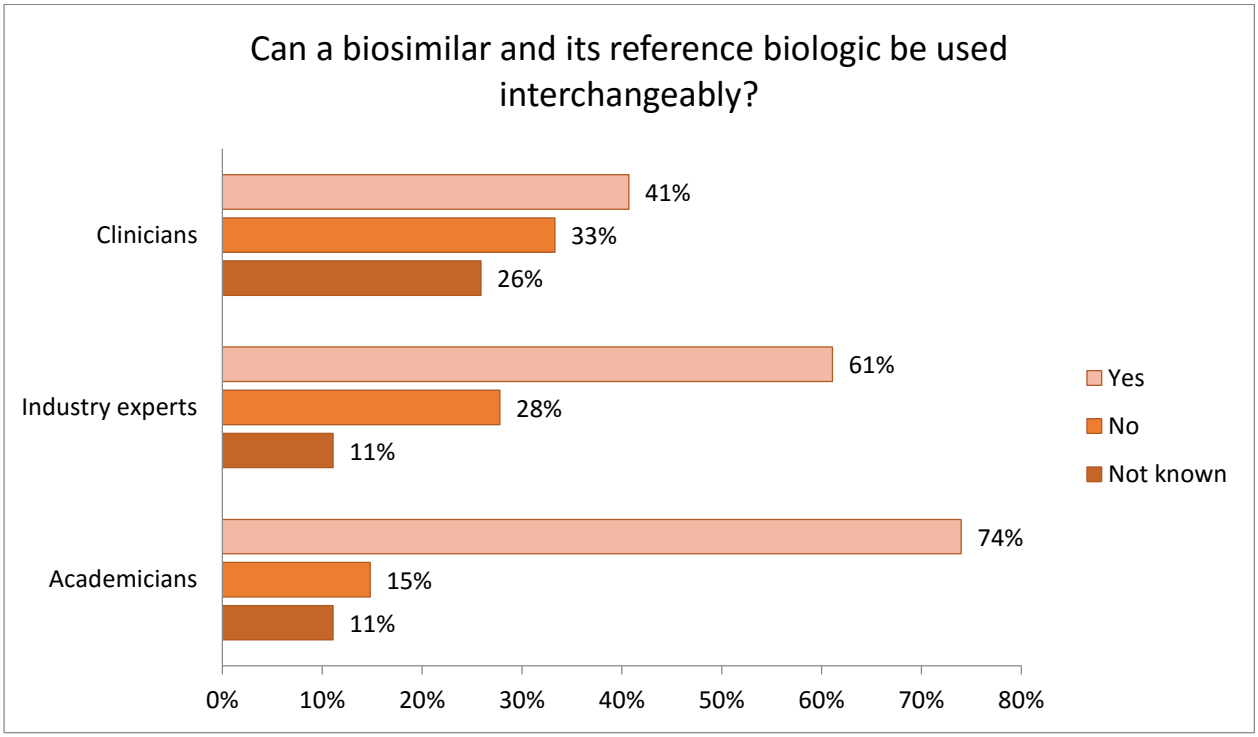

Figure 6.13 Interchangeability between the Biosimilar product and its Reference Biologic

Industry experts were further questioned regarding the ability to employ a different delivery device or container closure system for biosimilars compared to their relevant biologics. Their response is displayed in Figure 6.14.

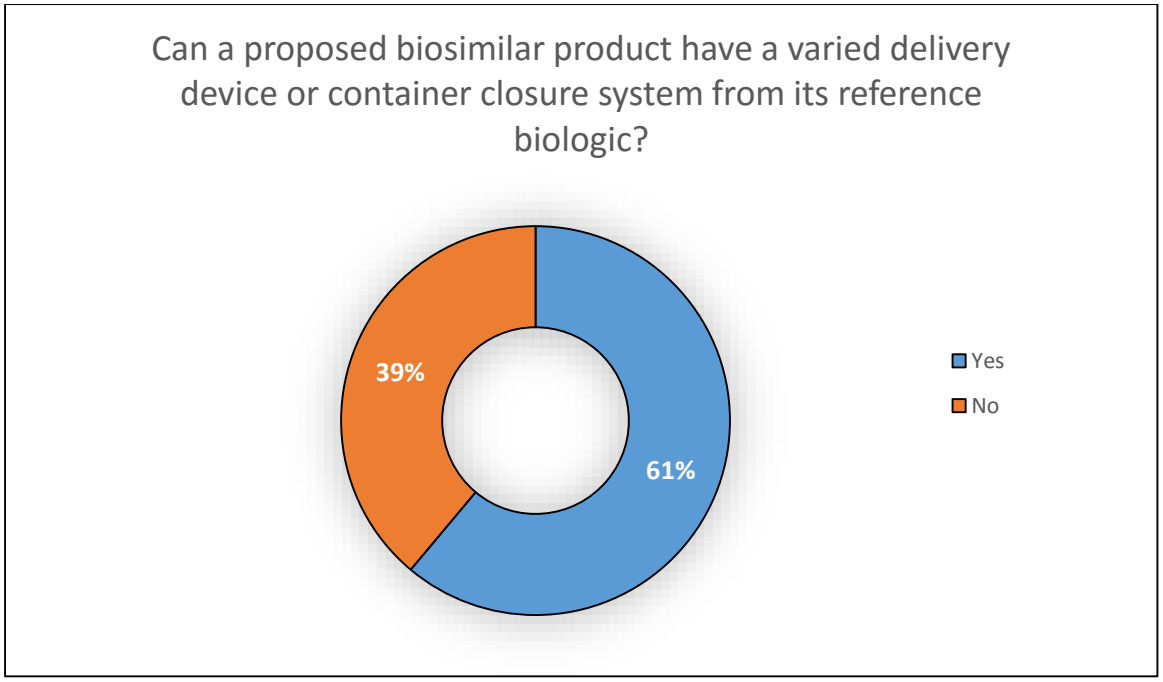

Figure 6.14 Utilization of separate delivery device or container closure system for Biosimilars compared to that of Biologics

The labeling requirements for newly introduced biosimilar products has been an issue of debate within the Bangladesh pharmaceutical industry, with current existing guidelines not providing any specific naming systems for biosimilars. With regard to what labeling guidelines should be followed, industry experts have provided the following suggestions:

I) Naming system designed with a strong reference to WHO, EMA or suitable guidelines from other reference countries.
II) Information on the reference biologic used as well as mention of any differences in manufacturing and expiry dates.
III) Use of Extensible Markup Language (XML) practices in structured product labelling to facilitate a both human and machine readable format.
IV) Execution of surveys within the local population to determine the most effective biosimilar naming system which will be suitable and unambiguous to patients.
V) Execution of pre-marketing surveys by biosimilar manufacturers within the local population to determine a suitable and unambiguous name for their product.
VI) Ensure that the new biosimilar name does not have more than two consecutive letters in common with the reference biologic.

Industry experts were surveyed regarding how biosimilar manufacturers can provide evidence to clinicians regarding the reliability of their product, especially in terms of non-immunogenicity. Their feedback is illustrated in Figure 6.15.

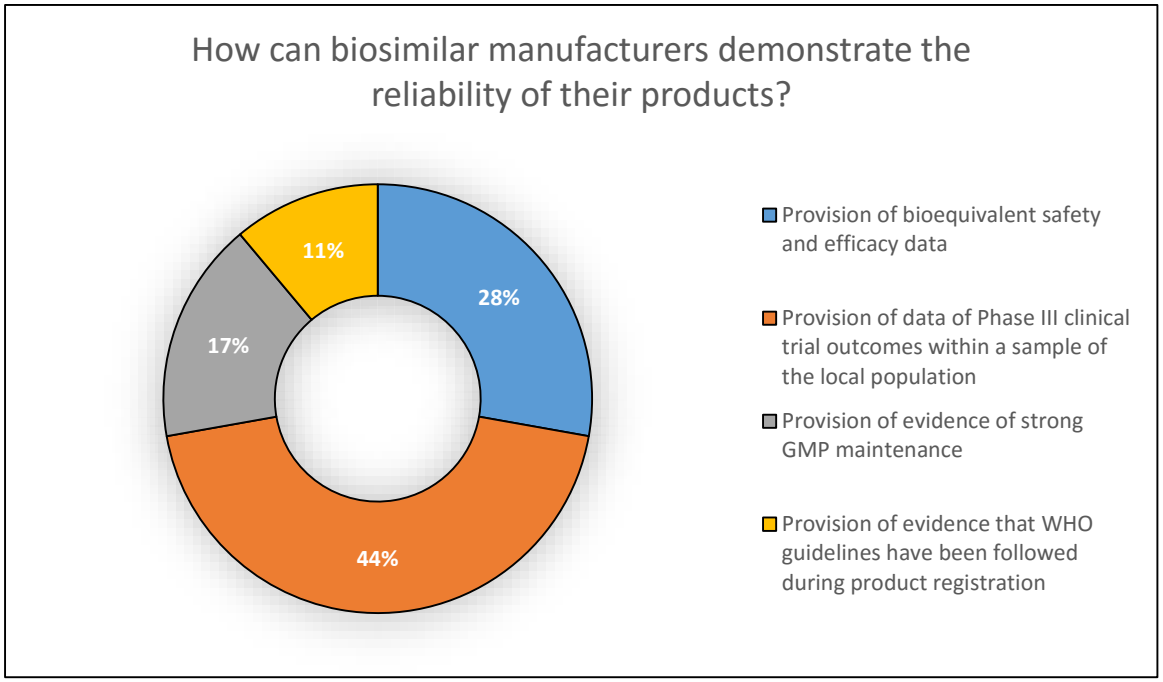

Figure 6.15 Methods of Biosimilar reliability demonstration by Manufacturers

Around **89 percent** of industry experts surveyed voted for the necessity for manufacturers and prescribers to make available the data regarding the biosimilar's development process, clinical efficacy and safety to patients; a practice that would essentially promote patient welfare and reliance on manufacturers and clinicians.

Finding a suitable method for educating patients on the benefits and applications of biosimilars would significantly aid in biosimilar acceptance during drug therapy. Industry experts were asked to recommend the most effective methods for patient counseling on biosimilars. Their responses are compiled and presented in Figure 6.16.

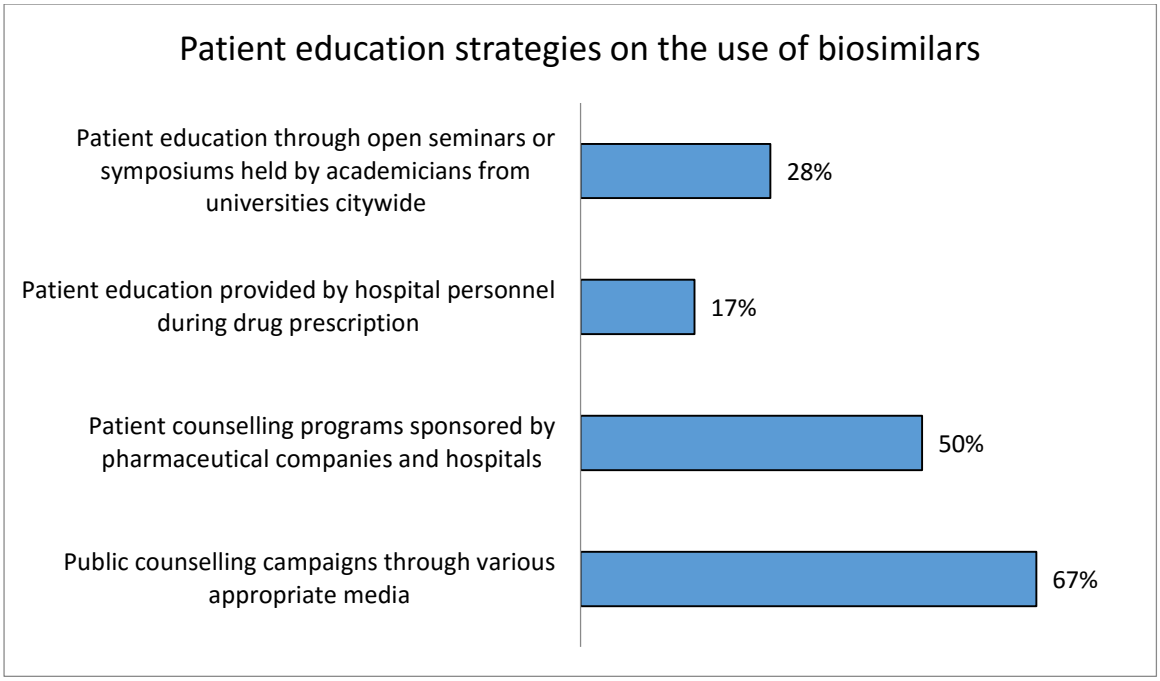

Figure 6.16 Patient Education strategies on the use of Biosimilars

An appropriate price strategy for biosimilars could significantly aid patient accessibility and adoption as well as bring in a meaningful amount of revenue for biosimilar manufacturers. Industry experts were surveyed on their opinions regarding how this pricing should be ideally strategized and their feedback constituted of the following recommendations:

I) Pricing strategy designed with a strong reference to WHO, EMA or suitable guidelines from other reference countries.
II) Pricing strategy optimized by researching into income distribution within the economy and patient purchasing capacity.
III) Pricing strategy designed with reference to the national pricing system for biologics, ensuring that the price of biosimilars is maintained at relatively lower costs.
IV) Pricing strategy designed with reference to the small molecule generic drug pricing framework.
V) Price strategy designed by pharmaceutical production oriented experts within the industry instead of one designed by the business executive body of the company.

With regard to ameliorating the availability of biosimilars in current national clinical practices, these drugs need to be commercialized at relatively lower costs from their reference biologics. Clinicians were requested for their opinion on the degree of price variation between biosimilars

and their innovator drugs, with the hope of consequently lowering patient healthcare costs and facilitating treatment. Their responses are presented in Figure 6.17.

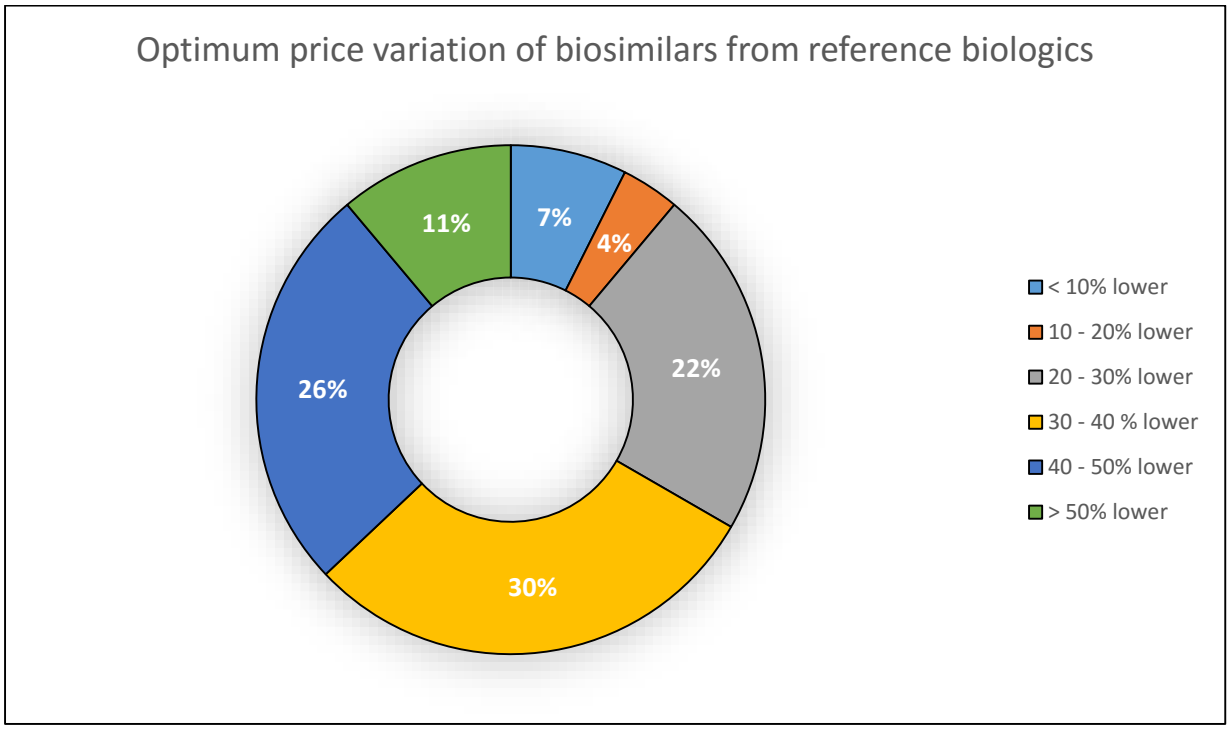

Figure 6.17 Optimum price variation of Biosimilars from Reference Biologics

Lowering the cost of production of biosimilars often conflicts with the need for pharmaceutical manufacturers to maintain an identical safety profile of the drug to that of the reference biologic. This spurs a debate between the necessity to improve patient accessibility by lowering prices and the vitality of maintaining quality of drug therapy by preserving the therapeutical properties of the drug. **67 percent** of academicians surveyed felt that the quality profile of the biosimilar should be prioritized over the drug pricing with the resolve to hold patient safety over other aspects of treatment.

Certain treatment programs in hospitals require individualized pediatric assessments when undergone by children. These programs play a major role in assisting with the healthcare of the child and their implementation in biosimilar medication applications could improve the adoption of such drug therapies in lower age demographics of the country. Academicians were surveyed for their opinion on the necessity of such programs and their feedback is displayed in Figure 6.18.

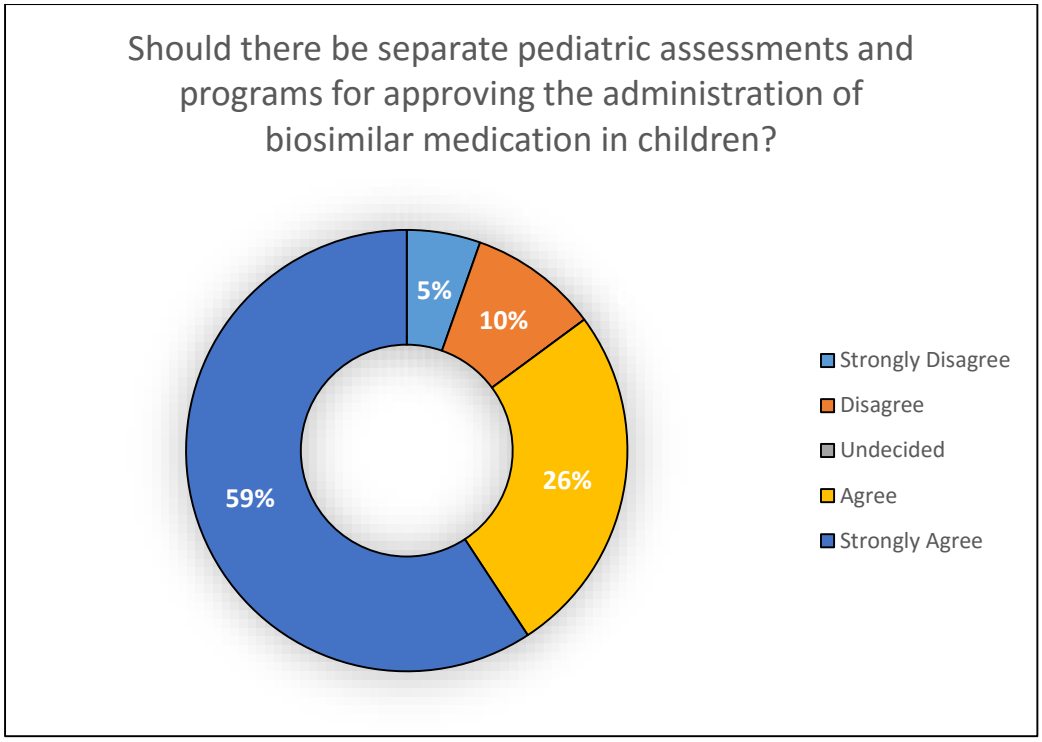

Figure 6.18 Need for pediatric assessments for approving Biosimilar drug therapy in children

Academicians from leading universities citywide also provided feedback on the presence of course material on biologics and/or biosimilars within the department undergraduate and postgraduate degree curriculum. Only academicians from departments where there was a scope of educating students regarding biologics and biosimilars were surveyed. Their responses were construed and presented in Figure 6.19.

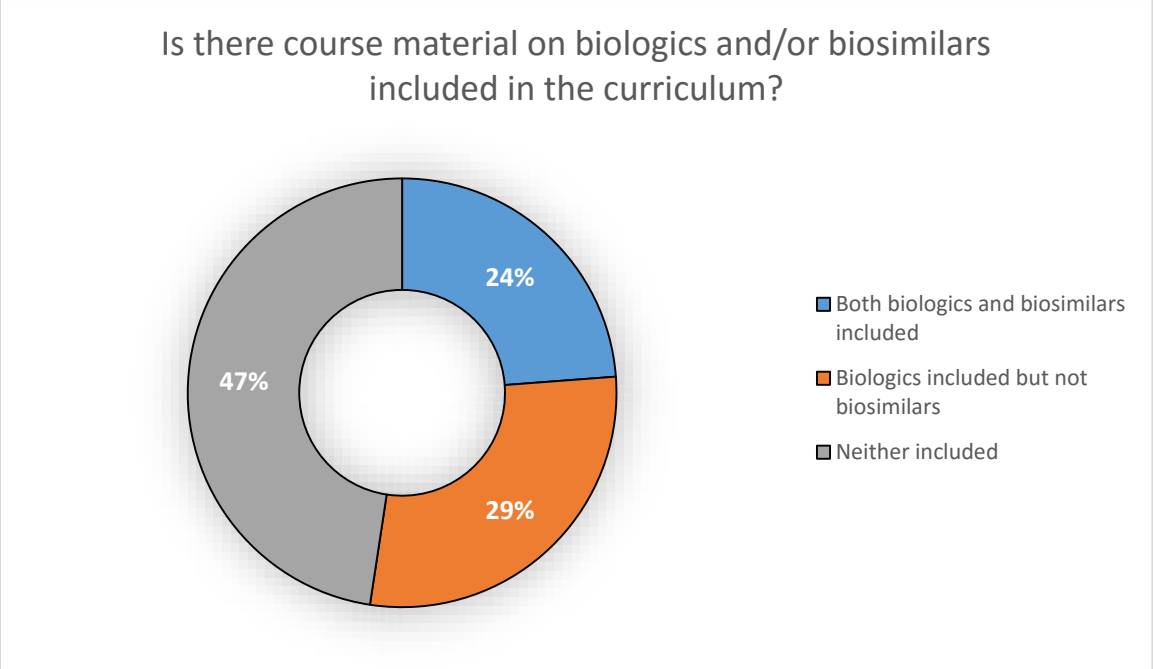

Figure 6.19 Presence of course material on Biologics and/or Biosimilars in university curricula

Most universities providing education on biologics and biosimilars had their own individual biotechnology departments or had incorporated courses within their pharmacy curricula to subsume these topics. The courses most frequently mentioned by the candidates of the survey included:

I) Pharmaceutical Biotechnology
II) Advanced Pharmaceutical Biotechnology and Biopharmaceuticals
III) Regulatory Affairs
IV) International Marketing
V) Bioinformatics

Research Question 4: Are Non- Comparable Biologics (NCBs) synonymous to biosimilars?

A clear perception of Non-Comparable Biologics is essential to distinguish them from biosimilars in terms of their safety and efficacy profile. Improving the understanding of the variations between the two would limit the number of low quality drugs reaching the Bangladesh drug market and subsequently, patients undergoing therapy within the country. Industry experts were asked if NCBs are synonymous to biosimilars. Their answers are presented in Figure 6.20.

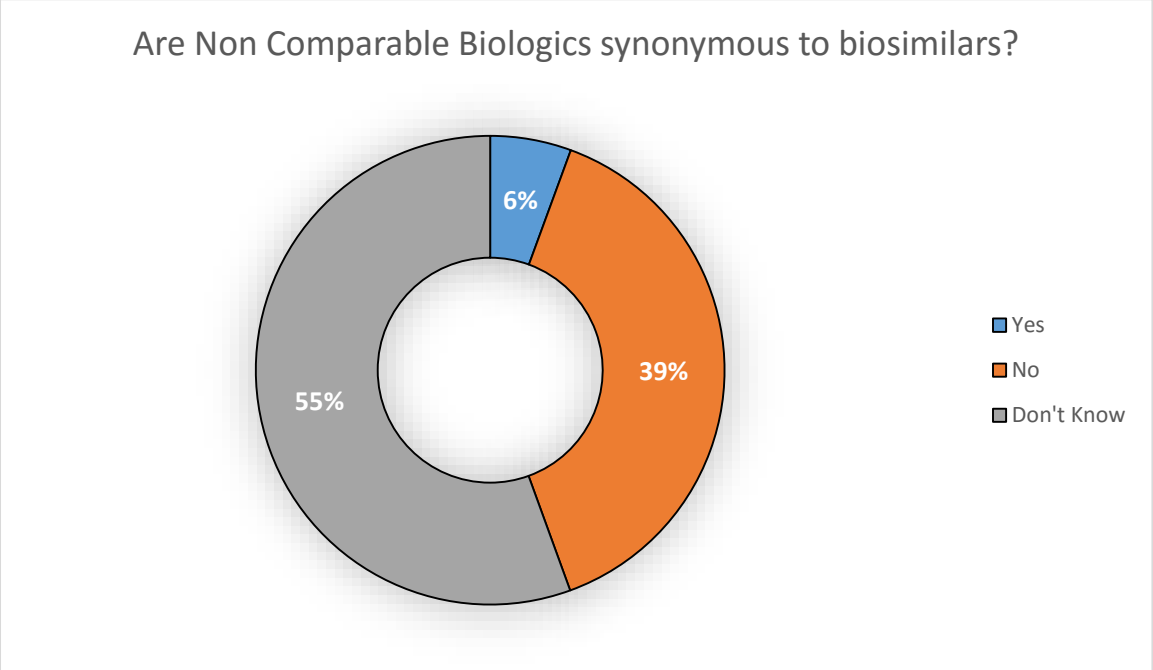

Figure 6.20 Addressing the understanding of NCBs among local Industry Experts

7. Analysis and Discussion of the Survey Results

The results obtained from each individual objective of the survey were analysed and interpreted to relate to the leading research questions. Discrepancies in data due to a lack of coherence and correlation among the survey answers were also identified.

Research Question 1: What is the status quo of the Bangladesh biologic and biosimilar drug industry?

The data in Table 6.1 shows that a majority of academicians (**53 percent**) and industry experts (**72 percent**) regard biosimilars as drugs possessing equivalent clinical properties as that of the reference drug molecules. Their stance mandates the need for biosimilars to display identical safety and efficacy profiles compared to their reference biologics after undergoing Phase I-III trials. Figure 6.1 backs the efforts by industry experts to make biosimilars a feasible concept of treatment for patients within Bangladesh, with a positive response being obtained from over **75 percent** of the experts surveyed. Negative responses were obtained from those industry experts who felt that the current accessibility to biologics treatment was satisfactory and no changes in regulatory guidelines were needed to facilitate a new branch of drugs. Data obtained in the succeeding graph (Figure 6.2) shows that there is good to high awareness of biosimilars among majority of clinicians within Dhaka city. It also shows that a high percentage of clinicians (**44 percent**) have a moderate to very low awareness of biosimilar medication, goading the need for better availability and spread of education on biosimilars within hospital settings. When analyzing the challenges involved in introducing biosimilars within the drug industry, the results obtained (Figure 6.3) show that both groups polarized towards the need for updated regulatory guidelines to facilitate the introduction of biosimilars into the Bangladesh drug industry. At the same time, there was also a high demand from industry experts for improved pharmacovigilance catering to biosimilar drugs while academicians stipulated the need to reduce any patient health related complications which may occur during substitution of biosimilars in therapy. Majority of individuals from both groups felt that the economic and societal consequences of biosimilar use would be insignificant if they were introduced after sufficient clinical testing and were regulated by standard guidelines. Present state guidelines however, were considered inadequate, with the data in Figure 6.5 showing that a large percentage of candidates (**28 percent**) were dubious regarding the strength of the current

biologic and biosimilar regulatory guidelines while majority of experts (**50 percent**) voted that the present national decree did not have biosimilar regulations clearly outlined. Even though the development period of biosimilars is lengthy, majority of both industry experts and academicians voiced that it was a hurdle worth overcoming (as seen in Figure 6.5), and had strong expectations regarding the prospects of biosimilar development within the national drug industry. The data in the pie chart (Figure 6.6) shows that the primary source of information for a majority of clinicians in Dhaka city is from medical conferences, closely followed by biotech companies and peer reviewed journal articles. This signals the need for a greater distribution of biosimilar education within these avenues to improve clinician awareness as well as making other sources such as the popular press and medical associations more prominent as biosimilar information resources.

Research Question 2: How can the introduction of biosimilars benefit the welfare of the people in Bangladesh?

As previously mentioned, we first compared the major drivers that would encourage doctors to endorse the prescription of biosimilars to those that would encourage local doctors. The results for general clinicians (Figure 6.7) show that majority (**61 percent**) favoured prescription of biosimilars due to its safety (as maintained according to the standards of the reference drug) as well as the lower price of the drug (**56 percent**) which facilitated its affordability to patients. The results for local clinicians (Figure 6.8) show that majority (**67 percent**) favoured prescription of biosimilars due to their lower prices and a large number of clinicians (**61 percent**) also supported biosimilar prescription given the assurance that Phase III trials of the drug had been performed within a sample of the local population. Maintenance of a proper national system of pharmacovigilance for biosimilars as well as an identical safety and efficacy profile to that of the original biologic were factors that were also given priority. Comparing the two sets of data, we interpreted that there was a higher prioritization by local physicians for lower valuation of the biosimilars opposed to the prioritization of drug safety by general clinicians. This indicates the greater need for the maintenance of greater accessibility of biosimilar medication to patients within Bangladesh. The greatest advantages of biosimilars, as seen from the data displayed in Figure 6.9 are that biosimilars pose to be beneficial in lowering healthcare costs for civilians undergoing treatment (voiced by **80 percent** of academicians and **83 percent** of industry experts), as well as the assurance of being able to treat the same indications as those remedied by the reference biologic (voiced by **35 percent**

of academicians and **44 percent** of industry experts). The possible advantages of a lower therapeutic dose or utilization of an administration route varying from the original biologic were less favoured by the candidates surveyed. Data from the chart created in Figure 6.10 show that a majority of industry experts (**67 percent**) strongly agreed that the quality profile of the biosimilar should be conserved within the standards of the reference molecule in order to maintain an appropriate biosimilar identity. Majority of industry experts (**57 percent**) also backed biosimilar development in light of their shorter approval process compared to that of the reference biologic (shown in Figure 6.11). The willingness of biosimilar prescription by clinicians (Figure 6.12) showed that majority of clinicians were positive (**19 percent** Likely**, 48 percent** Very likely **and 19 percent** Highly likely) to the likelihood of prescribing biosimilars if they were made readily available and accessible to them. Clinicians who voted that they were not likely to prescribe biosimilars felt that the medication posed a significant safety risk to patients.

Research Question 3: How can the adoption of biosimilars in the Bangladesh drug industry be facilitated?

Feedback obtained from clinicians, industry experts and academicians with regard to the interchangeability of a biosimilar product with its reference biologic (Figure 6.13) show a larger percentage of academicians (**74 percent**) and industry experts (**61 percent**) felt that biosimilar therapy was interchangeable with their innovative drug therapies and supported their promotion within the clinical setting. A comparatively higher percentage of clinicians (**26 percent**) within the city were doubtful regarding the interchangeability of therapy and **33 percent** of clinicians were against drug substitution, feeling that there were significant patient risks involved. With regard to the capability of using a different delivery device or container closure system for the biosimilar compared to those used for its innovator biologic, the results in Figure 6.14 reflects a larger percentage of industry experts (**61 percent**) disagreed to the premise on the grounds that a change in container or administration system would significantly affect the dosage uniformity and therapeutic effect of the drug. Those who agreed (**39 percent**) stated that a change in delivery device or closure system to a more suitable alternative could significantly promote the adoption of the biosimilar (which would then be termed as a "biobetter"). When considering the possible ways by which manufacturers can demonstrate the reliability of their product, mainly in terms of non-immunogenicity, the results obtained in Figure 6.15 show that a majority of industry experts (**44 percent**) suggested the provision of

Phase III clinical trial data in order to establish the reliability of the biosimilar product to clinicians. **28 percent** of industry experts also vouched that the non-immunogenicity of the drug can be demonstrated by providing strong safety and efficacy profile information on the biosimilar for reference in clinical practice. Patient education on the use of biosimilars can also be facilitated by several options, out of which the results in Figure 6.16 show that majority of industry experts (**67 percent**) primarily preferred the utilization of public counseling campaigns through various media outlets for effective patient guidance, followed by patient counseling programs funded by pharmaceutical manufacturers, hospital boards or clinicians (**50 percent**). Minority of industry experts (**17 percent**) surveyed supported patient education provided by hospital personnel during drug prescription on the grounds that it was time consuming and disadvantaged patients who needed medication in a state of emergency. With regard to the pricing strategy that should be employed for biosimilars, the feedback represented in Figure 6.17 show that a majority of clinicians (**30 percent**) opted for a more modest price discount of 30-40% for biosimilars and feel that it is suitable for ensuring sufficient patient cost savings as well as meeting the biosimilar's cost of production targets. Additionally, taking into account the varied compliance of medication of children compared to that in adults, responses represented in Figure 6.18 show that majority of the academicians interviewed were positive (**59 percent** Strongly Agree and **26 percent** Agree) that pediatric assessments were an important inclusion for the approval of biosimilar drug therapy in children within hospitals of the country. With context to whether undergraduate and postgraduate students were exposed to information on biologics and biosimilars, the results obtained from academicians (represented in Figure 6.19) showed that a large percentage of academicians (**53 percent**) vouched for the incorporation of knowledge on biologics within the curriculum of their respective universities, out of which **24 percent** voted having information on both biologics and biosimilars included. However, knowledge on biologics and biosimilars is not as predominant within several university curricula as voted by **47 percent** of academicians, urging the need for an updated revision of the syllabi to include a deeper understanding of this branch of drugs.

Research Question 4: Are Non- Comparable Biologics (NCBs) synonymous to biosimilars?

With regard to whether NCBs ae synonymous and can be substituted with biosimilars, results obtained from Figure 6.20 show that **39 percent** of industry experts surveyed disagreed that

they were identical to each other. However, the concept of NCBs was still vague among a large proportion of industry professionals (**55 percent**), a matter which could potentially decrease the quality of drug therapy within the country. Steps should be taken to tackle this problem immediately, prioritizing the need to raise awareness of NCBs among industry experts, clinicians, academicians and patients in order to preserve the integrity of future biodrug treatment programs.

8. Conclusion

Bangladesh continues to be one of the strongest frontier countries in the growth of pharmerging markets in the Asia Pacific, with an expected compound annual growth rate (CAGR) of 10.4% of its annual pharma sales by the end of the year 2017 (IMS Health, 2013). According to Bangladesh's Ministry of Finance, 5.2% of the country's GDP is utilized in its healthcare expenditure (as of 2016) with over 3600 pharmaceutical brands of Bangladesh internationally registered. The country's staggering population has not hindered its economic growth stability, its rise to becoming a lower middle income country from a lower income country (as classified by World Bank) nor its increasing health awareness through the successful development and propagation of health education programs and NGOs. There is currently a strong understanding of biosimilars within industries, hospitals and universities of Dhaka, backed by the strong awareness of its potential as a more prevalent option for patients undergoing biodrug therapies. However, present biosimilar regulatory guidelines set by the DGDA are very limited, especially with regard to their manufacture, presence of clinical data, naming and labeling, interchangeability and pharmacovigilance. All candidates surveyed have collectively agreed that the introduction of biosimilars would bring numerous benefits to the welfare of the people of Bangladesh. The data shows that a majority of these advantages would be in terms of improving the accessibility of medication (via lower costs and shorter registration processes) to patients needing biodrug therapy as well as offering a greater range of treatment options to clinicians. There is an increased demand on the drug authority to promote the transparency of safety and efficacy data of biosimilar drugs to both clinicians and patients, as well as approve biosimilars within the country only after they have undergone satisfactory Phase III trials within samples of the local population. Along with concurring with the requirement of an updated regulatory decree that differentiates between biologics and biosimilars (designed with reference to reputable international standards), candidates have also called for pricing strategies that will maintain the price of biosimilars significantly lower than their corresponding reference biologics, and campaigns to promote patient and clinician education on biosimilars. There is a need for import and export policies of biologics and biosimilars to be refined in order to promote the preservation of local biotech product manufacture, while not intervening on a patient's right to choose from a wider range of biodrug treatment options. The data also shows that clinicians are strongly encouraged to not compromise the quality profile of the biosimilar drug over its pricing when prescribing to patients, as well as to clearly state to their patients the

advantages and disadvantages between the biosimilar drug and its reference biologic (including any variations in side effects) before prescription. Furthermore, universities have taken initiatives to incorporate education on this branch of drugs into their curricula, with the hope of raising societal awareness on biologics, biosimilars and non-comparable biologics in the future.

9. Recommendations

The results that have been obtained from the survey may be used for future finalization and/or review of the existing national policy framework. The results may also be utilized to identify any areas of congruency the national drug policy may have with internationally recognized and accepted policy systems (such as the guidelines provided by WHO,EMA and USFDA). The results can be used to mark areas for development in the biologic and biosimilar drug industry, and feedback obtained from the study may aid in moulding prospective policies with a greater focus on the health and welfare of the people of Bangladesh. To conclude, success in meeting the demands and expectations for biosimilar introduction could see a revolutionary breakthrough in biological healthcare – the beginning of the age of biosimilars.

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Appendix

A1: Antibody – An antibody is a protein produced by the body's immune system when it detects harmful substances, called antigens. Examples of antigens include microorganisms (bacteria, fungi, parasites, and viruses) and chemicals.

A2: Hormone – Hormones are the body's chemical messengers. They travel in your bloodstream to tissues or organs. They work slowly, over time, and affect many different processes, including

- Growth and development
- Metabolism - how your body gets energy from the foods you eat
- Sexual function
- Reproduction
- Mood

A3: Insulin – A hormone made by the pancreas that allows your body to use sugar (glucose) from carbohydrates in the food that you eat for energy or to store glucose for future use.

A4: Cytokine – Cytokines are cell signalling molecules that aid cell to cell communication in immune responses and stimulate the movement of cells towards sites of inflammation, infection and trauma.

A5: Innovator drug - An innovator drug is the first drugs created containing its specific active ingredient to receive approval for use. It is usually the product for which efficacy, safety and quality have been fully established. When a new drug is first made, drug patent usually will be acquired by the founding company.

A6: Potency – The power of a medicinal agent to produce the desired effects.

A7: Monoclonal antibody- An antibody produced by a clone or genetically homogeneous population of fused hybrid cells.

A8: Nanobody - A **novel** class of **proprietary** therapeutic proteins based on **single-domain antibody fragments** that contain the unique structural and functional properties of naturally-occurring heavy chain only antibodies.

A9: Immunotherapy - The treatment of disease by inducing, enhancing, or suppressing an immune response. It is designed to elicit or amplify an immune response.

A10: Immunoconjugate - A complex of an antibody and a toxic agent (as a drug) used to kill or destroy a targeted antigen (as a cancer cell).

A11: Patent - A right, granted to an inventor, to *exclude* others from *making*, *using*, *selling* or *importing* an invention throughout the country without the inventor's consent.

A12: Interchangeability – In medicine, this refers to drugs that contains the same amount of the same active ingredients, possesses comparable pharmacokinetic properties, have the same clinically significant formulation characteristics, and is to be administered in the same way as the drug prescribed.

A13: Efficacy - The maximum response achievable from an applied or dosed agent. It is the ability of a drug product to produce the desired effect.

A14: Steam sterilization - Steam sterilization is a simple yet very effective decontamination method which is achieved by exposing products to saturated steam at high temperatures (121°C to 134°C). Product(s) are placed in a device called the autoclave and heated through pressurized steam to kill all microorganisms including spores.

A15: Phase III clinical trials: These are randomized controlled multicenter trials on large patient groups (300–3,000 or more depending upon the disease/medical condition studied) and are aimed at being the definitive assessment of how effective the drug is, in comparison with current 'gold standard' treatment. They involve a new treatment that's worked well in a small number of patients with a certain disease. Doctors compare the treatment with the standard of care for that disease. The goal is to find out if the new treatment is better than standard treatment and/or with fewer side effects.

A16: Anaphylaxis - Anaphylaxis is a potentially life threatening, severe allergic reaction and should always be treated as a medical emergency. Anaphylaxis occurs after exposure to an allergen (usually to foods, insects or medicines), to which a person is allergic.

A17: Pharmacokinetics - Pharmacokinetics, sometimes described as what the body does to a drug, refers to the movement of drug into, through, and out of the body—the time course of its absorption, bioavailability, distribution, metabolism, and excretion.

A18: Hypersensitivity - Hypersensitivity refers to excessive, undesirable (damaging, discomfort-producing and sometimes fatal) reactions produced by the normal immune system.

A19: Interferon - Interferons are a family of naturally-occurring proteins that are made and secreted by cells of the immune system (for example, white blood cells, natural killer cells, fibroblasts, and epithelial cells). Three classes of interferons have been identified:

1. alpha,
2. beta, and
3. gamma.

Each class has many effects, though their effects overlap. Commercially available interferons are human interferons manufactured using recombinant DNA technology. The mechanism of action of interferon is complex and is not well understood. Interferons modulate the response of the immune system to viruses, bacteria, cancer, and other foreign substances that invade the body. Interferons do not directly kill viral or cancerous cells; they boost the immune system response and reduce the growth of cancer cells by regulating the action of several genes that control the secretion of numerous cellular proteins that affect growth.

A20: Plasminogen - The inactive precursor of plasmin, occurring in plasma and converted to plasmin by the action of enzyme urokinase.

A21: Transgenic - Transgenic is a term that describes an organism containing genes from another organism put into its genome through recombinant DNA techniques. An example of

its usage is the term *transgenic organism*. A transgenic organism is one that contains a gene or genes which have been artificially inserted instead of the organism acquiring them through reproduction. A transgenic animal, for instance, would be an animal that underwent genetic engineering. It often contains material from at least one unrelated organism, e.g. from a virus, a plant, or from another animal.

A22: Pharmacodynamics - Pharmacodynamics (PD) is an area of pharmacology concerned with the relationship between a drug's concentration at the site of action and the resulting effect, and to measurement of that relationship within an individual or group. Factors influencing a drug's pharmacodynamics include the concentration of drug target and the signalling pathways downstream.

A23: Indication - a condition which makes a particular treatment or procedure advisable

A24: Contraindication - a specific situation in which a drug, procedure, or surgery should not be used because it may be harmful to the person.

1. Introduction

2. Critical Variables of Biologics and Biosimilars

3. Non-Comparable Biologics (NCBs)

4. Current status of the Bangladesh Pharmaceutical Industry

5. Methodology

6. Results

7. Analysis and Discussion of the Survey Results

8. Conclusion

9. Recommendations

References

Appendix